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Part I.—Original Articles.

POST-HYPOGLYCAEMIC ENCEPHALOPATHY IN SAKEL'S INSULIN TREATMENT.

By A. M. SPENCER, M.B., B.Sc., D.P.M.,

Deputy Medical Superintendent, Joint Counties Mental Hospital, Carmarthen.

INTRODUCED in 1933, Sakel's pharmacological shock treatment [Sakel (1935*a*, 1935*b*, 1938)] is now regarded as a valuable method of treatment in schizophrenia. The complications which may ensue during the treatment are, however, both numerous and dangerous, and may be classified according to the system predominantly affected as follows:

(1) The Respiratory System.
(2) The Cardiovascular System.
(3) The Nervous System.

Complications of the respiratory and cardiovascular systems are comparatively rare, acute pulmonary oedema being the most serious complication affecting the respiratory system, while acute myocardial failure is a rare fatal complication of the cardiovascular system. Complications of the nervous system, on the other hand, are frequent and, ranging as they do from mild conditions such as transitory aphasia to fatal prolonged coma, constitute the major hazards of the treatment.

A. NEUROLOGICAL COMPLICATIONS OF SAKEL'S TREATMENT.

While the condition known as prolonged coma is the commonest and most fully reported complication, a large number of other complications occur which indicate that damage to the central nervous system may vary from the slightest degree to the most profound. These complications may be classified according to the main presenting symptoms as follows:

(1) *Confusion.*—Slight degrees of confusion persisting for a few hours after interruption of the coma are common in practice and references to the condition are fairly frequent, e.g. Gillman and Parfitt (1938), Katzenelbogen *et al.* (1939), Coyne (1940), Kant (1940). Gillman and Parfitt (1938) mention

that " we have given intravenous sugar more than 300 times to patients who were not sufficiently conscious 30 minutes after the feed, usually with satisfactory results, but fairly frequently a certain amount of confusion, mild headache and malaise persists." These authors' comment on such cases is especially noteworthy—" great care should be ensured in such cases when deciding the duration of the next shock, for we believe such conditions are often forerunners of delayed recovery of a serious kind."

(2) *Stupor.*—This may be present either alone or with one or more of the neurological abnormalities described below. In cases of the former type, the patient may be able to obey simple passive commands and the swallowing reflex is present. In practice, patients are frequently stuporose for short periods after the hypoglycaemia has been terminated, but Scherb and Stone (1938) mention a case in which the patient was stuporose for 8 hours, while a patient of Kant (1940) was " in a deeply clouded, stuporose condition " for 10 hours.

(3) *Aphasia.*—A number of cases have been reported in which aphasia occurred, usually of a transient character and clearing up after a few hours. Sometimes the aphasia occurs alone [Ruslander (1937–38), Goldman (1940), Golden (1937)] but it is usually accompanied by other abnormal nervous signs and symptoms. Schatner and O'Neill (1938) report the occurrence in a male patient of a paralysis of the right arm, which disappeared in 20 minutes, being accompanied by a motor aphasia which persisted for about an hour, while a female patient developed paralysis of the right arm and right leg, persisting for 3 hours and accompanied by a motor and sensory aphasia which cleared up in 1½ hours. Scherb and Stone (1938) record a case which had a transient aphasia accompanied by a severe headache, while Wortis, Bowman *et al.* (1937) noted three instances of transitory aphasia associated with facial weakness. A right hemiplegia and aphasia persisting for 10 hours in a patient aged 58 years is mentioned by Bond, Hughes and Flaherty (1939). Kant (1940) records that in a case of motor and sensory aphasia occurring on the 52nd day of treatment, the sensory features of the aphasia disappeared before the motor ones.

(4) *Dysarthria.*—A mild transient degree of dysarthria is frequently found in patients recovering from coma which has been interrupted by stomach tube, but Horwitz, Blalock and Harris (1938) record a case of an 8-year-old boy who was still stuporose 10 hours after intravenous injection of glucose. At 11 hours he was able to say Mama, but otherwise his speech was dysarthric.

(5) *Echolalia and Echopraxia.*—Horwitz, Blalock and Harris (1938) mention a case of post-hypoglycaemic stupor in which " as his physical condition improved and his speech returned, marked echolalia and echopraxia were observed."

(6) *Rotary movements.*—Read, Heilbrunn and Liebert (1939) record a case in which " we observed some peculiar rotary movements setting in 1 hour after interruption of shock. These movements lasted about 2 hours, and could be started in either direction by a slight push to the shoulder."

(7) *Diplopia.*—Schatner and O'Neill (1938) record three instances of diplopia in two female patients, who complained of double vision after interruption of hypoglycaemia and disappearing after about 20 minutes.

(8) *Facial paralysis.*—In addition to the facial paralysis occurring as part of a hemiplegia, Binzley and Anderson (1938) mention a case in which marked motor activity occurred during administration of glucose by vein, there being a shifting Babinski response and a paralysis of the right facial muscles.

(9) *Hemiplegias.*—Several instances of this complication are reported in addition to those mentioned under (3) above. The condition is usually transitory, clearing up after a few hours [Wortis, Bowman *et al.* (1937), Young *et al.* (1937), Golden (1937), Horwitz, Blalock and Harris (1938), Binzley and Anderson (1938), Bond, Hughes and Flaherty (1939), Schatner and O'Neill (1938)]. Read, Heilbrunn and Liebert (1939) cite a case in which a female patient developed a permanent left Hoffman sign, slight left facial palsy and increased reflexes. Palisa (1938) found among 170 cases, 6 patients who developed a right-sided hemiplegia, 1 with a left-sided hemiplegia, and 1 patient who showed an alternating right and left hemiplegia on no fewer than 5 occasions during a course of 55 shocks. The higher incidence of right-sided hemiplegias may be due to the greater development of the left cerebral hemisphere in right-handed people, rendering it more vulnerable to the adverse effects of insulin.

(10) *Epileptiform seizures.*—The term "convulsion" appears to be used loosely in the literature to cover both the generalized myotonic spasms, which may last up to 10 minutes, and the typical epileptiform seizure similar to that seen in idiopathic epilepsy. Read, Heilbrunn and Liebert (1939) state that 34 patients developed a convulsion at some time during the treatment. Three of these developed epileptic states, the first immediately, the second within 4 hours, and the third 15 hours after interruption of shock, but no details are given as to the exact nature of the convulsions, or whether they occurred while the patient was mentally clear or still in post-hypoglycaemic stupor. Similar accounts of convulsions are given by Scherb and Stone (1938), Young *et al.* (1937), Katzenelbogen (1939), Morrow (1938), Katzenelbogen *et al.* (1939), Kant (1940), Gillies (1937) and Gillman and Parfitt (1938), but in all these cases even where an epileptic fit is mentioned specifically it is difficult to be sure that intense generalized tonic spasms are not referred to. Typical major epileptiform seizures certainly occur, usually during the *early* stages of shock, sometimes before the patient has become unconscious, the effect frequently being that the unconscious patient spontaneously awakes owing to the rise in blood sugar following the seizure, but it is very difficult to see how such a seizure can occur in the absence of symptoms once the hypoglycaemia has been effectively interrupted, unless the patient develops "after shock" with its consequent fall in the blood sugar. Gillman and Parfitt (1938), however, report the case of a female patient who had a series of 15 fits at 10-minute intervals approximately 26 hours after interruption, during which time "she remained well."

The remaining complication of the nervous system is post-hypoglycaemic coma. It appears that the nervous complications cannot be divided into definite categories, but that they shade gradually from the mildest degree of mental clouding, through severe degrees, of such clouding, transient aphasias and paralyses, epileptiform convulsions and so on to the fully developed

post-hypoglycaemic coma, which, it will be seen, can itself be of varying degrees of severity, lasting from a few hours to several days. We turn now to a consideration of this condition.

B. POST-HYPOGLYCAEMIC COMA.

I. Synonyms.

Prolonged coma ; non-hypoglycaemic coma ; protracted shock.

II. Definition.

Post-hypoglycaemic coma [Goldman (1940)] occurs when the patient does not recover consciousness after sufficient glucose has been given either orally or intravenously ordinarily to terminate the coma. The condition is marked by varying degrees of hyperthermia ; hyperventilation, both hyper- and tachypnoea ; motor excitement, rigidity and tonic-spasms ; the Babinski response may or may not be present, but the corneal reflex can usually be elicited. The condition may persist for from a few hours to several days, and may result in (*a*) complete recovery, (*b*) recovery with varying degrees of cerebral damage, or (*c*) death (*Brit. Med. J.*, 1940).

III. Reported Cases.

De Morsier and Mozer (1936) first described the condition of post-hypoglycaemic coma in a morphine addict who was being treated with insulin. The first case occurring in Sakel's treatment was reported in the following year by Salm (1937). Following this a large number of reports have appeared. The following list is comprehensive except for articles in a few foreign journals which were not available for this study : Franke (1937), Gillies (1937), Kobler (1938), Leppien and Peters (1937), Molony and Honan (1937), Rossman and Cline (1937–38), Sherril and McKay (1937), Wortis, Bowman *et al.* (1937), Baker (1938), Binzley and Anderson (1938), Cammermeyer (1938), Doring (1938), Easton (1938), Finiefs (1938*a*), Gillman and Parfitt (1938), Horwitz *et al.* (1938), James, Freudenberg and Cannon (1938), Kastein (1938*a*, 1938*b*, 1938*c*), Lazell (1938), Lester (1938–39), Morrow (1938), Milch and Bolles (1938), McKendree (1938), Plattner (1938), O'Neill (1938), Scherb and Stone (1938), Telatin (1938), Timmer (1938), Baker (1939), Baganz and Laxon (1938), Braestrup (1939), Freed and Saxe (1939), Katzenelbogen (1939), MacKeith and Meyer (1939), Murphy (1939), Ribeiro and di Lascio (1939), Skaug and Hellem (1939), Theato (1939), Wortis and Lambert (1939), Yahn and da Silva (1939), Coyne (1940), Goldman (1940), Jansen and Waaler (1940), Kant (1940), Klein and Ligterink (1940), Vie and Opolon (1940), Polatin, Strauss and Altman (1940), Robinson and Robinson (1940), Abely and Feuillet (1941), Cleckley and Templeton (1941), Gralnick (1941), Abely and Feuillet (1942), Lawrence, Meyer and Nevin (1942), Proctor and Easton (1942), Schou (1942), Rivers and Rome (1944), Wechsler (1944).

IV. Modifications of Sakel's Hypoglycaemic Treatment.

It has been generally assumed that prolonged coma is caused by the induction of coma of such *depth* that irreversible changes have occurred in the brain. Unfortunately, the whole question of coma is confused in the literature owing to the differing standards of coma adopted by various authors and the frequent absence in published papers of the standard adopted by the writers. The present writer (Spencer, 1947) has reviewed the question, showing that Sakel himself used the term to cover all stages of unconsciousness from "sopor" (von Angyal, 1937) to unconsciousness and complete areflexia. The position would have been clarified considerably if a common standard of coma such as that adopted by Wilson (1937) of unconsciousness with Babinski responses and absent corneal reflexes had been generally agreed upon. Insufficient attention has also been paid to the influence of the *time* for which patients have been allowed to remain in coma, and the question has not been investigated as to whether prolonged coma is more likely to follow a deep coma lasting for a short time or a light coma induced for a longer period.

Owing to the dangers inherent in coma of Wilson's standard, medical and nursing staff shortages, etc., there has been a tendency in recent years for only the lighter types of unconsciousness to be induced, [e.g. Sherman, Mergener and Low (1941), Sandison and McGregor (1942)], although the duration of the hypoglycaemia remains about 5 hours. Early in 1945 a modified form of insulin therapy was instituted at the Joint Counties Mental Hospital, Carmarthen, as shortage of staff did not permit the practice of "deep-coma" therapy, and as events proved, this modified therapy cast considerable light upon the importance of the *duration* of unconsciousness in the production of prolonged coma.

Under this modified form of insulin treatment, the patients were given just sufficient insulin to induce unconsciousness after the lapse of some 3–4 hours from the time of the injection. This corresponds to the state called "sopor" by some authors. Frequently, but not invariably, the plantar responses become extensor during the period of unconsciousness, but the corneal reflexes are always briskly present. It will thus be seen that the depth of the coma is very light, and in no way comparable with the deep coma normally induced, in which the plantar responses are always extensor and the corneal reflexes either very sluggish or completely abolished. It was found, however, that once the "sopor" dose of insulin had been attained, the addition of a further 5 units was usually sufficient to extend the length of "sopor" to periods of from 1–4 hours, after which the patient spontaneously awoke. A total of 8 or 9 hours' hypoglycaemia might thus be induced, including 1–5 hours of light unconsciousness. *Duration of "sopor" replaced depth of coma as the object of the treatment.* Profuse perspiration might occur, but the sopor is never deep enough for tonic muscular spasms to be produced. Patients usually require about 30–40 units to produce sopors of 2–4 hours, but in the 50 patients to whom the treatment has been given, only 3 have required more than 50 units, there being one case requiring 70 units. It will thus be seen that the modified treatment is altogether lighter than Sakel's treatment.

It is no alternative to the latter treatment, and was only instituted because shortage of nursing and medical staff did not permit the giving of Sakel's treatment, and following the good results achieved by some workers with ambulatory insulin treatment [Polatin and Spotnitz (1942 and 1943).] While the results of the treatment do not compare with those obtained by Sakel, they are good enough to warrant its continuation until it can be replaced by the more thorough-going technique.

Despite the very light state of unconsciousness induced in this modified treatment, two of the first 30 patients treated developed prolonged comas, one of which terminated fatally. Case-reports of the two instances of prolonged comas will now be given, as they illustrate several features not mentioned previously in the literature.

V. Case Reports.

Case 1.—Female, aged 54 years.

Diagnosis.—Involutional melancholia.

The patient's illness dated from January, 1938. On 28.vi.38 she was admitted to the Maudsley Hospital. She showed the usual characteristics of involutional melancholia, intense depression, morbid feelings of guilt and unworthiness with somatic delusions, such as that she was suffering from venereal disease, and that consequently her bowels were stopped up. Prior to admission she had attempted suicide. She became more depressed during the following year, and was transferred to the City of London Mental Hospital on 29.vi.39. She remained unimproved, and was discharged to her husband's care on 7.x.39. A feature was noted at this time which became more marked later on. This was the conscious wish of the patient not to recover. She refused to co-operate in her treatment because she wished to die and not get well.

On 11.iii.41 she was admitted to the Joint Counties Mental Hospital, Carmarthen, her condition being as outlined above. Strong death wishes were prominent, and she stated that she could not and did not wish to recover. Electrical convulsive therapy was tried without effect. When the modified insulin treatment was instituted in the Hospital early in 1945, the patient was started on a course of treatment despite the length of her illness. On 12.iii.45 she was given an initial dose of 10 units. This was increased by 5 units each day, until she went into sopor 4½ hours after the injection of 35 units. During the following weeks the dose varied between 20–30 units, sopor usually lasting about 3–4 hours. She always awoke spontaneously, and at no time did her condition give rise to any anxiety. Her mental state gradually began to improve, inasmuch as her depression became less profound, but throughout she constantly expressed her wish to die and not to get better. Treatment was continued for 4 months and unexpectedly terminated as follows:

6.vi.45: Dose of insulin—20 units—sopor 4 hours. Spontaneous awakening. Took tea and supper and appeared her usual self.

7.vi.45: Dose of insulin—25 units—sopor 6 hours. She came round spontaneously, sufficiently to take a cup of tea, but was very confused, and almost immediately relapsed into a stuporose state in which she could be spoon-fed with fluids, but in which she was not conscious and was unable to speak. As this state showed signs of continuing, she was regarded as being in post-hypoglycaemic coma. Adequate fluids, intravenous glucose, sodium chloride, vitamins B and C were given in order to maintain her general condition, which was very good. Lumbar puncture was performed, but the fluid did not appear to be under increased pressure and its biochemical analysis gave normal results. Temperature 98·2° F., pulse 96, respirations 24.

8.vi.45: Her condition is unchanged except that at the end of the day her temperature has risen to 101·8° F. and her pulse, of good volume, is 118/minute. Respirations, 20/minute. Fluids have been continued and she takes well by spoon-feeding, being able to swallow easily. Her eyes are open, and one has the impression that she is just beyond being fully conscious. One feels that if she made

the effort she could become fully conscious, but her attitude is one of complete apathy and she is incontinent of urine. She remains mute. Her condition is most interesting and unusual. It appears as though she is deliberately willing herself to remain out of contact with reality, a condition in keeping with her frequently expressed wish to die.

9.vi.45 : Her condition remains unchanged. Treatment as before. General condition good. She continues to give the impression that she is deliberately refusing to regain full consciousness. She sits propped up in bed looking vacantly in front of her in a completely passive attitude. Temperature 102° F., pulse 110/minute, respirations 18/minute.

10.vi.45 : During the day her general condition has deteriorated considerably. She remains just " around the corner " from full consciousness, but her physical condition is causing concern. She has been given continuous " drip " saline to maintain the circulation and has had a transfusion of one pint of blood. Late in the day she became cyanosed, but this was relieved by oxygen given through a nasal catheter. Temperature 103° F., pulse 120, respirations 24.

11.vi.45 : Her heart failed finally at 1.0 a.m. Permission for a post-mortem examination was refused.

Comment on Case.

This case is interesting for two reasons :

(1) It proves conclusively that depth of coma is not necessarily the most important factor in the production of post-hypoglycaemic coma, but that the duration of hypoglycaemia may be of even greater importance. This patient's hypoglycaemic state was so light that she did not even develop extensor plantar responses, yet despite this, after a period of 6 hours' unconsciousness at the " sopor " stage she developed prolonged coma. The significance of this will be more fully discussed later.

(2) The psychological factor seemed to enter significantly into the outcome of the coma. This also will be discussed in detail later, but it may be said now that the patient's frequently expressed wish not merely to die (a passive wish), but her wish not to get better (an active wish), indicated such a powerful development of the Freudian death-instincts that she died when she need not have done so. In watching her attitude during her prolonged coma one was almost forced to the conclusion that the patient deliberately willed herself to death.

CASE 2.—Female, aged 24 years.

Diagnosis.—Paranoid schizophrenia.

This patient had been ill for 2 months before her admission to the Joint Counties Mental Hospital, Carmarthen, on 14.xii.45. Several near members of her family were below average in intelligence, but no cases of psychotic breakdown among them could be elicited. The patient had always been of a shy, introverted disposition, and no adequate external cause for her breakdown could be found.

Condition on admission.—During the interview her manner was pleasant and equable, but her answers to questions were frequently delayed owing to blockage of thought. Her level of general intelligence was definitely subnormal. She was unable to do the 100–7 test, she knew the number of pence in 1*s.* 9*d.*, but could not do the 3*d.*'s in 3*s.* 9*d.* and the 2*s.* 6*d.*'s in 15*s.* She had no knowledge of current affairs. She showed marked ideas of reference, and believed that people around her were constantly laughing at her. A number of non-systematized paranoid delusions were easily elicited. She believed that her parents were trying to rob her of some money which she had in the bank, and that her brother-in-law had tried to kill her with a pocket-knife on a number of occasions. She could give no reason for his wanting to do this except that he was against her.

She believed that her food in the hospital was being poisoned, and that one of the nurses wanted to kill her as she was in league with her parents. She was aurally hallucinated for a man's voice which abused her, but she would not discuss her hallucinations in detail. In view of her persecution at home and her hallucinatory experiences she had decided to commit suicide as soon as possible. There was mild incongruity between her thought processes and mood. She completely lacked insight into her mental state and believed that she was perfectly well.

Her physical state was satisfactory except that she had a raised blood pressure (178/94).

During the following 2 weeks she received a course of 7 electrical convulsions, as a result of which she was considerably less restless, although her schizophrenic thought processes remained the same, nor did she develop any insight into her condition. In view of her poor response to E.C.T. a course of modified insulin therapy as given to the previous patient (Case 1) was started on 7.1.46.

Responses to insulin.—The initial dose of insulin was 20 units, increased on succeeding days as follows until she developed sopor: 25, 30, 35, 40, 45, 50, 55, 60, 65, 70. On 70 units she went into sopor for the first time for the unexpectedly long period of $4\frac{1}{2}$ hours, from which she spontaneously awoke. In view of the length of this sopor, the dose was reduced the following day to 60 units. The injection was given at 7.0 a.m. and she went into sopor at 11.10. The sopor was quite light, although Babinski responses were present from 11.30–12 noon. Her condition was perfectly satisfactory and sopor was allowed to continue for 5 hours, i.e. until 4.10 p.m., at which time she was given 100 c.c. of glucose (40 per cent.) intravenously. Her sopor lightened further following this, but she did not regain consciousness. Twenty minutes later she was given a further 100 c.c. of glucose (40 per cent.) intravenously without effect and she was then judged to be in post-hypoglycaemic coma.

Her condition at this time differed remarkably from that seen in most cases of post-hypoglycaemic coma. She appeared to be asleep. Respirations were regular, deep and of average rate. Her pulse was regular, of good volume, although a little fast (90/minute). She did not perspire, and all her reflexes were normal. At no time did she show tonic extensor spasms. *She remained in this condition for 5 days.* Her general condition remained satisfactory throughout this time and never gave rise to any anxiety. Her treatment consisted of generous quantities of milk, water, sodium chloride, halibut oil (for vitamins A and D) and marmite (vitamin B) by stomach tube; ascorbic acid and vitamin B parentally to ensure absorption. Her temperature rose to 99·6° F. on the first day, but became normal on the second day and did not rise again.

At the end of the fifth day of coma she spontaneously awoke. Her speech was slurred for the first few hours and then rapidly improved. By the following day she appeared to be her normal self apart from a slight degree of confusion which persisted for 3 days, when it cleared up.

Condition 7 Days After End of Prolonged Coma.

Her mental condition has improved considerably compared with what it has been on admission. Most noticeably, all her paranoid delusions and hallucinations have disappeared and *she is completely amnesic for ever having held them.* She is considerably more alert and active than on admission, and spontaneously takes part in the ward activities. She is, however, still entirely lacking in insight into her mental state and has no idea why she had to come to the hospital. She is also amnesic for the whole of the period of her prolonged coma.

She remained in this condition until her discharge from hospital 3 months later. A follow-up 4 months after her discharge indicated that her parents considered that she was better than she had been for a number of years, and that she was doing her work on a farm perfectly satisfactorily, although she was still rather shy and reserved.

Comment on Case.

Like the preceding case, this patient illustrates the view that great depth of coma is not necessary for the production of post-hypoglycaemic coma, but that the *duration* of hypoglycaemia is of equal importance. This patient had

a period of 9 hours' hypoglycaemia, including 5 hours of sopor. Although the sopor was very "light," the hypoglycaemia was sufficiently long to produce irreversible changes in the brain which caused the post-hypoglycaemic coma, which was also of a superficial character.

VI. Aetiology of Post-Hypoglycaemic Coma.

(1) *Incidence of Post-Hypoglycaemic Coma.*

It is difficult to arrive at a satisfactory estimate of the incidence of the complication owing to the large number of unreported cases, and because the percentage incidence is frequently not given in those which are reported. In the present author's series of 146 cases the condition occurred 4 times (2·7 per cent.). Dussik (1936 and 1938) found it occurred 5 times in 5,000 treatments. In a survey of post-hypoglycaemic coma in 20 hospitals in U.S.A., Lester (1938–39) found a total of 25 examples among 1,173 completed insulin cases (2·1 per cent.). Kant (1940) had 9 cases in a series of 61 patients (15 per cent.); Goldman, 23 in a series of 108 patients (21·1 per cent.); Rivers and Rome (1944) 38 in a series of 225 patients (17·1 per cent.); while Schou (1942) found the high proportion of 127 out of 375 patients (30·1 per cent.). There seems to be no satisfactory explanation for these widely differing degrees of incidence.

(2) *Age and Sex of Patients.*

A review of the recorded cases indicates that the ages of the patients vary from 20–48 years, with the age group 20–30 years predominating. As the age of onset of schizophrenia is also chiefly in this age group, no significance would appear to attach to the age of the patient as far as liability to post-hypoglycaemic coma is concerned.

Among a sample of 96 cases in the literature, there were 52 males and 44 females, so that the sexes would appear to be equally subject to the condition.

(3) *Race and Climate.*

Post-hypoglycaemic coma has been reported from all countries where Sakel's treatment has been tried. In America, white and negro patients seem to be equally liable to the condition.

(4) *Type of Schizophrenia in Affected Patients.*

Catatonic, paranoid and hebephrenic types of schizophrenia are all reported, with the paranoid form predominating. The absence of cases of the dementia simplex type is probably due to the fact that these patients tend not to receive insulin treatment in view of the poor results obtained with such patients. Easton (1938) states that he had become increasingly wary of a certain type of patient, tall, asthenic, with cold, blue hands and feet, whom he had found to tolerate insulin very poorly. Lester (1938–39) believes that prolonged coma is due to the fact that a number of patients possess a constitution which is unable to withstand with average impunity a prolonged period of hypoglycaemia. No details are given, however, as to the type of constitution the author refers to.

That the condition is not restricted to schizophrenia is shown by the present author's case, Case 1, who was an involutional melancholic, while Cleckley and Templeton (1941) had two patients, one with a manic-depressive psychosis and the other with hysteria, who developed post-hypoglycaemic coma.

(5) *Dose of Insulin at which Post-Hypoglycaemic Coma Occurs.*

Analysis of 83 published cases in which is given the dose on which prolonged coma occurred gives the figures of the following table :

TABLE I.

Units of insulin	20–39	40–59	60–79	80–99	100–119	120–139	140–159	160–179
Number of cases	2	12	11	16	10	10	6	4
Units of insulin	180–199	200–219	220–239	240–259	260–279	280–299	300–324	325 +
Number of cases	2	4	1	1	1	—	1	4

While there may be a slightly greater proportion of cases in the 80–99 units group, in general the range of doses corresponds closely to that used in uncomplicated cases, and undue sensitivity to insulin, requiring the use of smaller doses than usual, does not appear to be of aetiological significance in post-hypoglycaemic coma.

(6) *Number of Daily Treatments after which Post-Hypoglycaemic Coma Occurs.*

In order to ascertain whether prolonged coma is more likely to occur at any stage in the course of the treatment, the 55 cases in the literature which give the necessary information were analysed to find :

(*a*) The day of treatment on which the initial coma occurred.

(*b*) The number of cases preceding the prolonged coma.

(*c*) The total number of treatments preceding the prolonged coma.

The results of the analysis are set out in the following table. To ensure that the table is arithmetically complete, it is necessary to know, in addition to

TABLE II.

(A) = Day of treatment of initial coma.
(B) = Number of comas before prolonged coma.
(C) = Total number of treatments before prolonged coma.

Case Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
(A)	6	6	—	4	2	—	—	9	21	5	4	30	8	5	4	4	—	14	5
(B)	3	5	21	—	3	—	—	6	1	1	2	1	14	1	11	36	35	2	4
(C)	9	11	21	4	5	7	21	25	22	6	31	22	6	25	40	44	16	9	—

Case Number	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37
(A)	—	—	—	9	13	10	6	8	10	13	12	6	14	6	12	5	2	—
(B)	30	16	7	6	12	25	4	9	3	5	23	1	—	28	5	9	7	—
(C)	—	24	20	27	25	35	10	17	13	18	35	7	28	34	17	14	9	55

Case Number	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55
(A)	—	6	—	—	3	3	11	8	6	—	—	5	6	4	3	—	6	—
(B)	—	2	—	—	1	1	6	26	5	—	22	2	5	1	2	—	11	—
(C)	52	8	18	19	14	4	17	34	13	6	41	7	11	5	5	7	17	6

the above factors, the number of non-coma treatments the patient received after the initial coma, but this information is not given in several of the articles, so that the table is not arithmetically complete.

These results are given in detail above as they show that in a certain proportion of cases there is a definite association between the occurrence of prolonged coma and the induction of coma after only a few days' treatment (Cases 1, 2, 4, 5, 10, 11, 14, 19, 26, 31, 36, 43, 47, 49, 51, 52, 53 and 55). The results may also be grouped as follows :

TABLE III.

Days	1–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40+
Number of patients whose *number of days of treatment before initial coma* fall into the opposite groups	11	19	9	—	1	—	1	—	—
Number of patients whose *number of comas preceding the prolonged coma* fall into the opposite groups	18	8	4	1	3	3	1	2	—
Number of patients whose *total number of treatments preceding the prolonged coma* fall into the opposite groups	3	16	6	11	5	3	3	2	5

This table brings out—

(1) That prolonged coma may occur at any time during the course of Sakel's treatment : 10 of 54 patients had received more than 30 treatment-days before their prolonged coma occurred, while 5 had actually received more than 40 daily treatments. Attention may be drawn particularly to these findings. While, as is seen below, the majority of cases of prolonged coma occur through coma being induced too rapidly in the course of treatment, yet a considerable proportion (20 per cent.) of patients go through more than 30 days' treatment normally and then suddenly develop prolonged coma. Constitutionally, they can hardly be different on the day they develop prolonged coma from what they were on the previous 30 days. By the 30th day of treatment the coma dose of insulin is usually standardized, and yet unexpectedly the patients develop post-hypoglycaemic coma. Rivers and Rome (1944) point out that in a large proportion of their 38 patients who developed prolonged coma deeper stupors had previously been observed, and yet the patients had not previously developed prolonged coma. It was the existence of this group of patients which led to the attempt to determine whether the probably shorter-acting intravenous insulin would give rise to fewer neurological complications than the usual subcutaneous or intramuscular insulin (Spencer, 1947).

(2) That, despite the above, the majority of cases of prolonged coma occur in the early days of the course of treatment and especially, as noted above, if coma is induced only a few days after the commencement of the treatment. Eleven of 41 patients had less than 5 treatments before coma was induced, and 30 of 41 patients had less than 10 treatments. In addition, of 40 patients, 18 had received fewer than 5 comas and 26 fewer than 10 comas when they went

into prolonged coma. Of 41 patients, 3 had received less than 5 treatments in all and 19 less than 10 treatments in all before post-hypoglycaemic coma set in. Since prolonged coma can occur at any time during the course of treatment, other factors must obviously play a part, but the table shows the danger of increasing the dose of insulin so rapidly that coma is reached by the 5th or 10th day. Thirty-nine of 41 patients who developed prolonged coma had coma induced within 15 days of commencing the treatment, and it is probable that had coma been induced over a period of, say, 21 days, the incidence of prolonged coma would have been considerably less, since only 2 of the same 41 patients had had coma induced over periods of larger than 15 days. It is not merely a question of increasing the daily dose of insulin by equally small doses in all cases, as each patient's reaction to insulin is peculiar to that patient, but of determining the daily increase according to the development of the signs of hypoglycaemia in each patient so that coma will be reached by about the 21st day. Because of this, Lester's (1938–39) finding that a series of patients who developed prolonged coma after less than 4 comas had been given a daily increase of 12·5 units, whereas a similar series of patients who developed the condition on, as an average, the 20th coma had been given a daily increase of 10·6 units, is not significant.

VII. Pathology of Post-Hypoglycaemic Coma.

(1) Morbid Anatomy.

In the reports in the literature of post-mortem examinations of patients who have died from post-hypoglycaemic coma, attention has been devoted almost exclusively to the brain, from the pathology of which the various authors have attempted to deduce the cause of the condition. Microscopic studies of other organs have only been reported in a few cases, but as Dunner, Ostertag and Thanhauser (1933), Enstene and Altschule (1931), Ernstene *et al.* (1935), Jorgensen (1940), Tannenberg (1939) and Terron and Malesani (1939) have shown in animal experiments, the heart, skeletal muscles and the liver may also show marked changes, and the cause of prolonged coma may be found in dysfunction of some organ other than the brain, despite the primarily neurological clinical picture seen in the condition. The morbid anatomy may therefore be considered under the various systems and organs which are affected by hyperinsulinism in human subjects:

(*a*) The Central Nervous System.
(*b*) The Cardiovascular System.
(*c*) The Respiratory System.
(*d*) The Liver.
(*e*) The Pancreas.
(*f*) The Suprarenal Glands.
(*g*) The Kidneys.

This will be followed by a review of the results of animal experiments and an examination of the theories as to the cause of prolonged coma which have been advanced as a result of the study of the morbid anatomy.

(A) *The Central Nervous System.*

As has been mentioned, pathological studies of patients who have died from prolonged coma have been confined mainly to the brain, which has also been closely studied in animals subjected to large doses of insulin. A number of the articles in the literature have been reviewed by Lawrence, Meyer and Nevin (1942), who, however, did not restrict themselves to a consideration of changes found in patients dying in post-hypoglycaemic coma during Sakel's treatment, but included also cases of spontaneous hypoglycaemia due to adenomata of the pancreas, and also diabetics who had developed hypoglycaemia through an overdose of insulin. As the latter patients, especially, were not physically normal at the time when they became hypoglycaemic, as are the patients undergoing Sakel's treatment, reports on their morbid anatomy will not be considered.

The general pathological findings in the central nervous system in the reported cases may be summarized as follows : The neurones may suffer from general or localized ischaemia, which may be so severe that the entire neurones may disappear. The neurones of the frontal, temporal and occipital lobes are more frequently affected than those of other lobes, with the heaviest incidence of damage falling on the Cornu Ammonis and its Sommer sector in ticular. There is a reactive response, either proliferative or degenerative, on the part of the glial elements, while the blood vessels show a proliferative endarteritis, with perivascular exudation, neoformation of blood vessels, pseudocalcification of the media and sometimes thrombosis in the cerebral vessels. These changes will now be considered in detail as they affect the various parts of the brain.

(1) *Meninges.*

The condition of the meninges has not usually been reported on, but Ferraro and Jervis (1939*a* and 1939*b*) noted that in one case they were normal with marked congestion of the meningeal blood vessels, while Gralnick (1941) found the same congestion of the blood vessels in meninges which were transparent to the naked eye.

(2) *External Appearance of the Brain.*

De Morsier and Mozer (1936) found no naked-eye changes in the brain of a morphine addict who had died in prolonged coma following treatment with insulin, as did Ferraro and Jervis (1939*b*) in 4 schizophrenia patients. Similar findings have been reported by Cammermayer (1938), Jacob (1939), Jansen and Waaler (1940) among others. Gralnick (1941), however, found that the brain of a patient dying after 10 days of prolonged coma was oedematous with narrow, shallow sulci.

(3) *Internal Structure of the Brain.*

(a) *Neurones.*—There is a considerable degree of unanimity in the reports of the changes found in the neurones by various authors, although some confusion exists through the use of different stains and a somewhat loose termino-

logy to describe the changes found. Reports of detailed histological studies of the brain have been published by, *inter alia*, Cammermayer (1938), Doring (1938), de Morsier and Mozer (1936), Ferraro and Jervis (1939*a* and 1939*b*), Gralnick (1941), Jacob (1939), Jansen and Waaler (1940), Kastein (1938*a*, 1938*b*, 1938*c*), Kobler (1938), Leppien and Peters (1937), Lawrence, Meyer and Nevin (1942), Salm (1937), Scherb and Stone (1938), Timmer (1938), and MacKeith and Meyer (1939).

As regards the changes in the individual neurones, these have been found to vary from the slightest to the most profound, from chromatolysis, shrinking, vacuolysis, swelling of the nucleus, eccentric placing of the nucleus, homogeneous cytoplasm, swelling of the Nissl bodies, to complete disappearance of the neurones. On the other hand, the neurones might be shrunken, deeply stained, with irregular nuclei and distorted dendrites, or elongated and triangular with sharp edges, the cytoplasm being homogeneous and eosinophilic, the nucleus eccentric—Spielmeyer's ischaemic degeneration.

The distribution of these changes in the neurones varies according to different authors, although some areas are more frequently reported as being affected than others. Cammermayer (1938) found that the superficial sub-pial layers were the most affected, but that generally the cortical changes had no elective character. Usually, while almost every neurone in the cortex might appear to be more or less affected, the portions of greatest devastation were frequently limited to areas about 1 cm. sq. The frontal, parietal and occipital lobes were more frequently markedly affected than other areas [Cammermayer (1938), Ferraro and Jervis (1939*b*), Gralnick (1941), Leppien and Peters (1937), MacKeith and Meyer (1939), and Salm (1937)], and in particular the Sommer section of Ammon's horn appeared to be unusually vulnerable. As regard the layers of the cortex, the more superficial layers were more affected than the phylogenetically older lower ones. Brodman's third layer seemed to be electively affected in a number of cases, producing an effect of pseudolamination. Cells around the calcarine fissure were particularly well preserved in a case of Doring (1938), which led the author to ascribe a vascular origin to the condition.

In the *basal ganglia* similar changes to those occurring in the cerebral cortex have been described by Cammermayer (1938), Ferraro and Jervis (1939*a* and 1939*b*) and Leppien and Peters (1937). As a rule, however, the changes in the basal ganglia were not as profound as those in the cortex.

In the *midbrain* and *medulla oblongata* some nerve cells are usually affected, but only to a mild degree compared to the changes in the cortex [MacKeith and Meyer (1939)].

In the *cerebellum* Ferraro and Jervis (1939*b*) and Gralnick (1941) found that the Purkinjë cells were deeply involved, numerous cells having completely disappeared. Of those that remained, the nuclei showed marked alterations ranging from chromatolysis to vacuolization and colliquation. Similar lesions were found in the inferior olive. In MacKeith and Meyer's (1939) case, however, the changes in the cerebellum were comparatively slight, the Purkinjë cells being somewhat paler than usual and the lipoid content of the neurones in the olivary body being probably a little increased.

It appears from the above review that the effects of hyperinsulinism upon the part of the brain depend upon the phylogenetic age of the part. The phylogenetically young portions, especially the highly developed occipital, parietal and frontal lobes appear to be particularly vulnerable. Of the layers of the cerebral cortex, the more superficial layers, and especially Brodman's third layer, appear to be more easily affected than the deeper, older layers. On the other hand, the phylogenetically older portions of the brain, the medulla and midbrain appear to be affected to a much more limited degree.

(b) *Neuroglia.*—All elements of the glial tissue react to the damage sustained by the neurones in prolonged hypoglycaemia. In the published reports attention is usually devoted to the microglia, the reaction of which is usually of a proliferative type, as shown by Ferraro and Jervis (1939*a* and 1939*b*), Leppien and Peters (1937), and Scherb and Stone (1938). The reaction may, however, be of a degenerative kind. Ferraro and Jervis (1939*b*) had one case in which the neuroglia showed amoeboid changes and clasmatodendrosis throughout the entire cortex. Hypertrophic changes in the microglia and red cells were observed in areas of major destruction of the neurones. MacKeith and Meyer (1939) and Lawrence, Meyer and Nevin (1942) have drawn attention to the marked changes which occur in the macroglia in addition to those to which the microglia is subject. The use of Holzer and Globus-Cajal preparations is necessary to show fully the proliferation of the macroglia, and the use of Nissl's stain only by most other workers probably accounts for the little attention the macroglia have received, as they do not stain well with the latter stain. The outstanding feature of MacKeith and Meyer's (1939) case was the great mobilization and proliferation of the macroglia affecting mainly the sub-pial layer, and to a varying degree the white cerebral and cerebellar matter and the globus pallidus.

(4) *The Blood Vessels of the Brain.*

Two of Ferraro and Jervis's (1939*a*) 5 cases showed no changes either macroscopic or microscopic in the blood vessels, but these cases are exceptional and difficult to explain. In most of the reported cases all the coats of the arteries appear to be affected, but the heaviest incidence of damage falls upon the endothelium [Cammermayer (1938), Ferraro and Jervis (1939*a*, 1939*b*), Gralnick (1941), Jansen and Waaler (1940), Kastein (1938*a*, 1938*b*, and 1938*c*) and Salm (1937)]. The walls of the arteries become greatly thickened owing to proliferation of the cells with narrowing or even obliteration of the lumen. This proliferation is most marked in the endothelium, but it is also shared by the adventitial cells. The nuclei are swollen, and the chromatin granules are darkly stained and increased in numbers. Some cells show varying stages of karyokinesis. Thrombi, secondary to the proliferation of the intimal cells, are frequently seen, as is also diapedesis of both erythrocytes and leucocytes. Perivascular haemorrhages also occur by rhexis. Cammermayer (1938), MacKeith and Meyer (1939) and Lawrence, Meyer and Nevin (1942) also found pseudo-calcification in the media of the pallidal vessels. The degree of vascular change is in direct proportion to the degree of change

in the neurones and is most marked in the areas of greatest devastation, in which many of the neurones have been completely destroyed. It is this close association between the degrees of vascular and neuronic change which has led several authors to postulate a vascular cause for the changes in the nerve cells. Ferraro and Jervis (1939*a*, 1939*b*) noted that the degree of vascular damage was also directly proportional to the quantity of insulin the patient had received, and found extreme vascular damage only in cases which had received very high doses of insulin.

Another change noted by most of the above authors is that of neoformation of blood capillaries, and here again the process was in direct proportion to the amount of cellular damage in the nervous system.

As regard the veins, several authors have found thrombosis affecting veins of various sizes, while Kastein (1938*c*) describes a case in which the superior longitudinal sinus was thrombosed.

(B) *Changes in Systems other than the Central Nervous System.*

Jansen and Waaler (1940) and MacKeith and Meyer (1939) appear to be the only authors who have made a detailed study at autopsy of organs other than the brain in fatal cases of prolonged coma. This is unfortunate, as such a study would probably shed some light on the problem as to whether the vascular or neuronic changes in the brain are primary. If the vascular changes were found in all the capillaries of the body the vascular hypothesis might be true, whereas if it were found that they were restricted to the brain, it would be presumptive evidence that the neuronic damage was primary and the vascular changes secondary in character.

(1) *Heart.*

Jansen and Waaler (1939) found only slight changes in the myocardium, while MacKeith and Meyer (1939) noted that the cavities were enlarged with flattened columnae carneae. No microscopical examination was apparently made in either case.

(2) *Lungs.*

Any changes in the lungs which might be due to the action of the insulin are usually masked by the terminal congestion of cardiac origin or pneumonia from which the patients finally die [Jansen and Waaler (1940), Salm (1937)]. Cammermayer (1939) noted the presence of "pneumonic infiltration," while Timmer (1938) found congestive haemorrhages. These were apparently not investigated microscopically, and it is interesting to speculate whether they were of the same nature as the haemorrhages usually found in the brain and described above.

(3) *Liver.*

Fatty degeneration of the liver was noted by Cammermayer (1939), Jansen and Waaler (1940), Kastein (1938*c*) and Timmer (1938). MacKeith and Meyer (1939) found only "very great congestion."

(4) *Pancreas.*

Jansen and Waaler (1940) found considerable change in the pancreas, but ascribed it to post-mortem autolysis. In MacKeith and Meyer's (1939) case there was no superficial evidence of disease of this organ.

(5) *Suprarenal Glands.*

The only reports of examination of the suprarenal glands are those of Schereschewsky, Mogilnitsky and Gorjaewa (1929) and Jansen and Waaler (1940), who in 4 cases found a large increase in the lipoid content of the cortex. This finding is of interest in view of the close association of the suprarenal cortex with carbohydrate metabolism, and of the administration by several authors of the hormone of the suprarenal cortex to patients suffering from post-hypoglycaemic coma.

(6) *Spleen.*

Salm (1937) noted that the spleen was moderately enlarged in one of his cases.

(7) *Kidneys.*

MacKeith and Meyer (1939) found on microscopic examination of the kidneys that they showed "widespread ischaemic degeneration of the glomerular arterioles and capillaries." There were numerous areas of cortical necrosis, corresponding to whitish patches already seen with the naked eye. These were probably secondary to the severe arteriolar degeneration. The kidney changes were recent; pyelonephritis could be excluded, but the authors were doubtful as to their significance. It may be that they were analogous to the changes seen in the cerebral blood vessels, and that the areas of cortical necrosis correspond to the areas of neuronic devastation so frequently found. If this explanation be correct, the vascular theory as to the primary cause of the changes in the brain in prolonged coma would be confirmed.

(c) *Brain Pathology in Animal Experiments in Hyperinsulinism.*

The results in experiments on animals, usually dogs, cats and rats, given large divided doses of insulin over periods of days and weeks approximate so closely to the results found at post-mortem examination of patients who have died from prolonged coma during Sakel's treatment that no purpose would be served by reviewing the literature on the subject in detail. Instead, attention will be concentrated on any additional information which may be elicited under the more controlled conditions under which animal experiments can be conducted. The following papers have been consulted for this study: Schereschewsky, Mogilnitsky and Gorjaewa (1929), Stief and Tokay (1932), Dunner, Ostertag and Thanhauser (1933), Tani (1935), Schmid (1936), Baker and Lufkin (1937), Sherril and MacKay (1937), Massazza (1938), Weil, Liebert and Heilbrunn (1938), Accornero (1938), Roizin (1939), Baker (1939), Appel,

Alpers, Hastings and Hughes (1939), Winkelman and Moore (1940), Finley and Brenner (1940), Gellhorn, Packer and Feldman (1940), Tyler and Ziskind (1940) and Ziskind and Tyler (1940).

Two factors which the results of animal experiments appear to elucidate are: (1) the possibility that the changes in the central nervous system described by various authors following fatal hyperinsulinism may be due to post-mortem changes, and (2) the relationship between the dosage of insulin employed and the degree of cerebral damage found at autopsy.

Baker and Lufkin (1937) gave insulin to rabbits under similar conditions to those of Sakel's hypoglycaemic treatment and killed the animals 5 days after the cessation of treatment. Microscopic examination revealed "no cell alterations of pathological significance and only an occasional haemorrhage into the brain or meninges. Our experimental observations would, therefore, seem to add weight to our impression that in the human cases, the cellular alterations were most likely of a post-mortem nature." Against this, however, we have the reports of a number of authors, e.g. Weil, Liebert and Heilbrunn (1938), Stief and Tokay (1932 and 1935), Finley and Brenner (1940), Winkelman and Moore (1940) and Roisin (1939), who found marked pathological changes in brains which had been fixed in formalin immediately the animal died. As in the case of Schmid (1936), Baker and Lufkin found such little evidence of abnormality owing to the low dose of insulin employed, and to the fact that their animals did not die in hypoglycaemia.

Several authors discuss the relationship between the dosage of insulin, the severity of hypoglycaemic symptoms and the degree of cerebral damage found post-mortem. Tani (1935) found that the severity of the post-mortem changes did not run parallel with the number of fits the animal had had during hypoglycaemia. In some cases with 10 fits no changes were found, while in others severe changes were found after only a few fits. Tani believes that this difference is related to differences in degree of curvature of the stem arteries. Appel *et al.* (1939) also failed to find such a relationship; one animal which had 56 convulsions showed no post-mortem changes in the brain, while others who had had fewer convulsions showed moderate degrees of ischaemia. Similarly, these authors found no direct relationship between the dosage of insulin employed and the severity of the post-mortem changes. Weil, Liebert and Heilbrunn (1938) found such a relationship, and thus rabbits which "received the largest number of units also showed the most marked histopathological changes. With doses up to approximately 60 units visible disease of the neurones was not produced; from 70–150 units somewhat more marked changes were seen, and with from 200–400 units severe damage was produced. The number of seizures alone is without significance as an indicator of the histopathological changes. What counts is the cumulative effects of repeated injections of large single doses of insulin."

The finding that the number of hypoglycaemic convulsions bears no relation to the degree of cerebral damage is in harmony with the work of Winkelman and Moore (1940), who found that even large numbers (up to 20) of cardiazol-induced convulsions produced little or no change microscopically in the central nervous system.

Tyler and Ziskind's results agree with those of Weil, Liebert and Heilbrunn (1938), as they found that the larger the dose of insulin used, the greater was the incidence of brain damage found post-mortem. "However," these authors add, "irrespective of the insulin dose, brain damage did not occur unless the animals were kept in the 'medullary stage' of hypoglycaemia for at least 100 minutes." This time-factor in the production of cerebral damage by hypoglycaemia appears to have been investigated by Tyler and Ziskind only, other authors taking account solely of the dosage of insulin employed. In the same year Ziskind and Tyler (1940) produced 3 groups of animals showing varying degrees of cerebral damage by the use of increasing doses of insulin. The groups were: (1) Those with variable degrees of cortical damage only; (2) thalamic preparations; and (3) midbrain preparations. The authors comment: "The demonstration of a gradient effect by insulin on the central nervous system may have a very significant bearing on insulin-shock treatment. The same effects as those now obtained may occur with milder but more prolonged degrees of hypoglycaemia, capable of affecting the higher centres but sparing the lower medullary centres. This would remove the present hazards of the treatment." Unfortunately, this is not borne out by experience, as Cases 1 and 2 of prolonged coma reported above show. For want of a more definite standard, it may be said that it is the total number of milligram/minutes of hypoglycaemia to which the tissues are subject which determines the degree of cerebral damage, and a moderate degree of hypoglycaemia unduly prolonged will have a great, if not greater adverse effect as a large dose acting for a correspondingly shorter time.

It is interesting to note that Schereskewsky, Mogilnitsky and Gorjaewa (1929) found many degenerative changes in the suprarenal glands, in addition to those in the nervous system, including the ganglion cells and neurones of the sympathetic system.

(D) *Causes of Brain Damage Following Hyperinsulinism.*

A number of theories have been advanced as to the cause of the pathological changes in the brain following hyperinsulinism.

(1) The *vascular theory* is that the blood vessels are primarily affected by the hypoglycaemia, and as a result of the endothelial proliferation, venous and capillary thromboses, perivascular exudation and diapedesis of red blood corpuscles, the blood supply to the neurones is interfered with, and the cells undergo changes varying from slight swelling to necrosis as a result. This theory is subscribed to by Doring (1938), Ferraro and Jervis (1939*a*, 1939*b*), Jacob (1939), Jansen and Waaler (1940), Leppien and Peters (1937) and Kastein (1938*b*), although in another paper (1938*c*) the last author prefers a "toxic-metabolic" origin. In favour of the vascular hypothesis is the focal character of the pathological changes, which often have a definite circulatory distribution, although in animal experiments Winkelman and Moore (1940) and Stief and Tokay (1932, 1935) found that almost every cell in the nervous system was affected.

(2) The *anoxic theory* is similar to the above, but attributes the pathological changes to intracellular anoxia rather than to diminished oxygenation due

to a reduced blood supply from the affected blood vessels. MacKeith and Meyer (1939), Ferraro and Jervis (1939*a*, 1939*b*), Weil, Liebert and Heilbrunn (1938) mention this hypothesis, which is based on the histological similarity between the effects of hypoglycaemia, and anoxia. Lawrence, Meyer and Nevin (1942) review points of similarity between the two conditions, but as these authors point out, it has been abundantly shown, e.g. Damashek, Myerson and Stephenson (1935) and Himwich, Bowman, Wortis and Fazekas (1937), that in hypoglycaemia there is no lack of oxygen in the blood, but an inability on the part of the tissues to utilize that oxygen owing to a deficiency of glucose in the cells resulting from the hypoglycaemia.

(3) The *toxic-metabolic theory* mentioned by Kastein (1938*c*), Ferraro and Jervis (1939*b*) and Jacob (1939) is that the insulin has a direct histotoxic action on the cells of the nervous system, but in the absence of experiments upon the effects of insulin upon isolated tissues, this remains an hypothesis.

(4) The *oxyachrestic theory* has already been mentioned in connection with the anoxic theory. The word oxyachrestia has been coined by Lawrence, Meyer and Nevin (1942) to emphasize that although the blood contains sufficient oxygen in hypoglycaemia, the tissues are unable to utilize the oxygen owing to a deficiency of the substrate-glucose. This possibility was mentioned by Ferraro and Jervis (1939*a*) among other authors. The word oxyachrestia is inadequate, as it gives no indication as to the cause of the cell's inability to use oxygen. A better term would be *aglucia*, as aglucaemia is already used for an absence of glucose from the blood, so aglucia would refer to an absence of glucose from the tissue-cells (*cf.* anoxaemia—anoxia). Terminological finesse apart, the theory has probably more supporting evidence than those given previously. This evidence will be reviewed in the section on Clinical Pathology, as a considerable amount of work has been done on cellular respiration in hypoglycaemia, especially by Himwich, Wortis and their associates.

It may be noted in passing that all the theories outlined above seek the cause of the pathological changes in the brain following hypoglycaemia in the brain itself, either in the neurones or the blood vessels. This is probably because detailed post-mortem attention has usually been restricted to the brain, especially in human subjects. As has been mentioned above, only two authors, MacKeith and Meyer (1939) and Jansen and Waaler (1940) give detailed reports of the examination of other organs. Yet hypoglycaemia of the severity met with in Sakel's treatment probably affects all tissues throughout the body, and it may well be that the *cause* for the pathological changes in the nervous system lies, not in that system, but in some other system in the body. This becomes the more possible when the complexity of carbohydrate metabolism is borne in mind. It is interesting to note in this connection that Jansen and Waaler (1940) and Schereschewsky, Mogilnitsky and Gorjaewa (1929) found degenerative changes in the cortex of the suprarenal glands after hyperinsulinism, and in view of the part the adrenal cortex is now known to take in carbohydrate metabolism, it may be that the cause of the cerebral changes may be found in the suprarenal gland and not in the brain. Certainly in future post-mortem examinations in cases of prolonged non-hypoglycaemic coma, a detailed microscopic examination should be made of every organ in the body.

In view of the marked *biochemical* changes which occur in hypoglycaemia and which have been fairly well studied (see next section), and the possibly equally marked biophysical changes which have scarcely been investigated, it is possible that the cause of the pathological changes following hypoglycaemia can never be fully understood from a study of the resulting morbid anatomy, but the study of such morbid anatomy should be as comprehensive as possible.

(2) Clinical Pathology.

In considering the clinical pathology of prolonged coma, the study of the physiological changes which occur during hypoglycaemia is as important as the study of any abnormalities found during the prolonged coma itself. This is because prolonged coma is the end-result of one or more processes which have been going on while the patient has been in hypoglycaemia, and an examination of those processes rather than of the end-result itself may yield the clue as to the cause of the condition. Clinical pathological findings which have been reported during prolonged coma will, therefore, be considered first, after which the physiological changes induced by hypoglycaemia will be reviewed.

Attention has been directed chiefly to the behaviour of the various constituents of the blood, cerebrospinal fluid, etc., during prolonged coma, and in the following review the constituents which have been reported upon will be described separately.

(a) *The Blood.*

(1) *Blood Sugar.*

Soon after prolonged coma was first described, it was recognized that the condition was not accompanied by a low blood sugar, as pointed out by Robinson and Robinson (1940). Very high blood-sugar values such as 280 mgm. per cent. [Molony and Honan (1937), Wortis and Lambert (1939)], 520 mgm. per cent. [Theato (1939)], 295 mgm. per cent. [Horwitz *et al.* (1938)], 576 mgm. per cent. [Ribeiro and di Lascio (1939)] and 230 mgm. per cent. [James, Freudenberg and Cannon (1938)] have been reported. It must be noted, however, that these high blood-sugar values have been found at examinations undertaken at sporadic intervals; frequently only a single estimation has been made during the course of the prolonged coma. Braestrup (1939) found a blood sugar of 155 mgm. per cent. 90 minutes after intravenous interruption, but this had dropped to 30 mgm. per cent. 75 minutes later, so that a high blood-sugar finding is not invariable in the condition. The only report in the literature in which regular blood estimations at fairly frequent intervals were done is that of Proctor and Easton (1942), who found that the blood sugar fluctuated rapidly between 46 mgm. per cent. and 320 mgm. per cent., and did not settle to within normal limits until the patient's clinical condition had markedly improved. It is possible that more intensive investigations would reveal a similar condition in other patients. It is indicative of a serious derangement of carbohydrate metabolism, and a satisfactory explanation of it is difficult to find. On the basis of Himsworth's (1939) " head of pressure "

theory of the function of the blood-sugar level, it might be thought that the previously glucose-starved cells may be able to utilize glucose supplies under high pressure, but that the attainment of the high level sugar necessary temporarily exhausts the blood-sugar level-maintaining mechanism, so that the blood sugar drops. As the blood-sugar level-maintaining mechanism recovers, so the blood sugar rises to a high level again, only to fall once more as the mechanism again becomes exhausted. This would account for the rhythmical rise and fall in the blood sugar dramatically shown in the chart in Proctor and Easton's report.

(2) *Blood Chloride.*

Compared with the normal 365 mgm. per cent. [Samson Wright (1945)] the blood chloride usually appears to be reduced in prolonged coma. Goldman (1940) reports a "relatively low" blood chloride, while Young, Young and Roucek (1937) found a value of 275 mgm. per cent.; Kant (1940), 209 mgm. per cent. These low values are probably due to excessive loss of chlorides in the profuse perspiration which is such a characteristic of post-hypoglycaemic coma, and indicates the need for maintaining an adequate chloride intake either by mouth or intravenously.

(3) *Blood Urea.*

In the 3 cases in which the blood urea has been estimated, it also appears to be on the low side. Goldman (1940) found a value of 19 mgm. per cent., Scherb and Stone (1938) one of 24 mgm. per cent., and O'Neill (1938) one of 16 mgm. per cent.

(4) *Blood Calcium and Phosphorus.*

In view of the tetanic nature of the myotonic spasms in prolonged coma, the carpo-pedal spasm which is present during the spasms and the ease with which they can be initiated by external stimuli, it might be thought that they were due to a calcium deficiency. Goldman (1940), however, who investigated the levels of blood calcium and phosphorus in prolonged coma, found only values within normal limits.

(5) *Blood Carbon Dioxide.*

Franke (1937) reported that in one of his cases of prolonged coma the carbon dioxide combining power of the blood was 50 volumes per cent., while in a case of Horwitz, Blalock and Harris (1938) the much lower figure of 22 volumes per cent. was found.

(6) *Arterio-venous Oxygen Difference.*

No reports have been published on this important factor in prolonged coma following Sakel's treatment, but Himwich, Bowman and Fazekas (1940) investigated it in a diabetic who died in prolonged coma following an overdose of insulin. The average arterio-venous difference in the oxygen content

of the cerebral blood was 2·76 volumes per cent., compared with the normal difference of 7·43 volumes per cent. This low value is similar to that found during insulin hypoglycaemia, and indicates that in prolonged coma the cerebral tissues are unable to utilize the oxygen supplied to them despite the fact that the necessary glucose substrate is now circulating in the blood.

(7) *Blood Concentration.*

Quantitative studies in the concentration of the blood in prolonged coma do not appear to have been made, but, amongst others, Goldman (1940) "early recognized that blood concentration was a feature of this reaction because the blood drawn for sugar determinations was thick and dark." Probably the excessive loss of fluid in the profuse perspiration and salivation to which patients in prolonged coma are subject is sufficient cause for the haemoconcentration.

(8) *Blood Counts.*

There appears to be a mild leucocytosis in post-hypoglycaemic coma. Murphy (1939) found a white cell count of 15,000, with 78 per cent. polymorphonuclears, 12 per cent. large lymphocytes, 8 per cent. small lymphocytes and 2 per cent. basophils. McKendree (1938) reported a white cell count of 13,400 with 84 per cent. polymorphonuclears and 16 per cent. lymphocytes. Wechsler (1944) found a leucocytosis of 10,800, and Theato (1939) one of 20,600. Reports of erythrocyte counts are restricted to one by McKendree (1937), whose patient had a haemoglobin value of 70 per cent. and 3,520,000 erythrocytes per c.c., and one by Theato (1939), in whose patient the figures were 90 per cent. and 5,000,000 respectively.

(9) *Blood Culture.*

Murphy (1939) cultured some blood from one of his patients in post-hypoglycaemic coma but the result was negative.

(B) *The Cerebrospinal Fluid.*

(1) *Pressure of C.S.F.*

With a few exceptions the pressure of the cerebrospinal fluid has been found to be normal, but unfortunately the number of manometric readings reported in the literature has been few, and most authors appear to have estimated the pressure from the rate at which the fluid escaped at the time of lumbar puncture. The following authors found normal C.F.S. pressures: McKendree (1938), O'Neill (1938), Horwitz, Blalock and Harris (1938), Goldman (1940), Cleckley and Templeton (1941), Gillman and Parfitt (1938) (one case), Read, Heilbrunn and Liebert (1939), Wortis and Lambert (1939), and Gralnick (1941), who did manometric readings at regular intervals throughout the course of a prolonged coma, found that the pressure was "low." On the other hand, Murphy (1939), Binzley and Anderson (1938), Braestrup (1939), and Proctor and Easton (1942) found slightly increased pressures. These

last findings may have been due to the patient being in a state of muscular tension when the lumbar puncture was performed. It appears, however, that the intracranial pressure is not raised in prolonged coma, a finding which is all the more interesting in view of the quietening effect which withdrawal of 10–20 c.c. of cerebrospinal fluid has upon a patient in the restless phases of the condition.

(2) *C.S.F. Sugar.*

Compared with the reports of Horwitz, Blalock and Harris (1939) and Goldman (1940), who found no increase in the C.F.S. sugar, high values were found by the following authors: Molony and Honan (1937), 300–360 mgm. per cent.; Murphy (1939), 122 mgm. per cent.; James, Freudenberg and Cannon (1938), 300 mgm. per cent.; Cleckley and Templeton (1941), 100 mgm. per cent.; Binzley and Anderson (1938), 105 mgm. per cent.; Gillman and Parfitt (1938), 135 mgm. per cent.; Ribeiro and di Lascio (1939), 223 mgm. per cent.; Abely and Feuillet (1942), 114 mgm. per cent.; but Braestrup (1939) reported the low figure of 55 mgm. per cent.

These very high values are often higher than the level of the blood sugar [Molony and Honan (1937)], and probably indicate the disturbed condition of carbohydrate metabolism in prolonged coma [Proctor and Easton (1942)].

(3) *Oiher C.S.F. Constituents.*

Brief reports on other constituents of the C.F.S. such as the chloride and protein content have appeared, e.g. Kant (1940), O'Neill (1938), but they appear to be present within normal limits.

(c) *The Urine.*

As would be expected with the abnormally high blood-sugar values found in prolonged coma, several workers, e.g. Scherb and Stone (1938), O'Neill (1938), Horwitz, Blalock and Harris (1938), Binzley and Anderson (1938), Gillman and Parfitt (1938), found sugar (up to 4 per cent.) in the urine, but as a rule, acetone and diacetic acid were absent. Apart from this finding and again indicative of deranged carbohydrate metabolism, the urine appears to be normal.

From the above review, it will be seen that investigations into the chemical pathology of prolonged coma have been inadequate both in range and intensity. The only clue to the cause of the condition which they afford is that there is undoubtedly a marked derangement of carbohydrate metabolism as shown by the widely fluctuating blood sugar [Proctor and Easton (1942)], the reversal of the usual ratio of the sugar levels in the blood and cerebrospinal fluid and the presence of sugar in the urine. Carbohydrate metabolism is not yet fully understood, but the endocrine system certainly plays a part in it, and it may be that the cause of post-hypoglycaemic coma lies in the effect of prolonged hypoglycaemia on some gland such as the pituitary or suprarenals, rather than on the neurones of the brain. As a result of such action, the

gland is unable to function properly when glucose is administered, carbohydrate metabolism is deranged, the brain, dependent as it is entirely upon carbohydrate for its metabolism, is unable to utilize the glucose now circulating in the blood and the patient remains in coma.

VIII. Physiological Changes in Hypoglycaemia.

It has been shown in the preceding section that the only positive finding in the chemical pathology of post-hypoglycaemic coma is that there is a profound derangement of carbohydrate metabolism which continues in spite of the administration of adequate carbohydrate. As the carbohydrate mechanism returns to normal, so the patient's clinical condition improves (Proctor and Easton, 1942). Too much attention has probably been paid to the effects of hypoglycaemia upon the nervous system, and too little to its effects upon the known stages of carbohydrate metabolism. In this review of the physiological changes in hypoglycaemia an attempt will be made to determine whether an adequate cause can be found for the derangement of carbohydrate metabolism. It would appear that this derangement is primary, and that the irreversible changes which are found in the brain in prolonged coma are secondary to it, but that once those irreversible changes have occurred *nothing* can reverse them, and that the patient's clinical improvement mentally is due to undamaged portions of the brain taking over the functions of the cells in which irreversible changes have taken place. It will be seen, therefore, that methods of therapy for prolonged coma which are based upon the pathological findings in the brain are unlikely to be successful in view of the irreversibility of the changes found there. If the exact point at which the carbohydrate mechanism becomes deranged can be found, a form of therapy might be devised to correct matters at that point. Better still, means might be found by which the derangement could be avoided.

Much remains unknown about carbohydrate metabolism, but the following scheme, adapted from Samson Wright (1945), summarizes our present knowledge.

(1) *Intestine*, glucose and amino-acids are absorbed and pass to the liver.

(2) *Liver* converts—

(i) Glucose → glycogen → glucose.

(ii) Amino-acids → non-nitrogenous residues and urea.

(3) *Blood glucose* formed from liver glycogen and non-nitrogenous residues of amino-acids.

(4) *Insulin* acts on—

(i) Liver, stimulating glycogen formation.

(ii) Liver, inhibiting glucose formation from non-nitrogenous residues of animo-acids.

(iii) Tissues, increasing glycogen storage and carbohydrate utilization.

(5) *Adrenaline, sympathetic N.S., thyroxine* stimulate conversion of liver glycogen to glucose.

(6) *Adrenocortical hormone* stimulates glycogen formation in liver and inhibits new glucose formation.

(7) *Diabetogenic hormone of pituitary gland* acts on—

(i) Liver, stimulating conversion of glycogen into glucose.

(ii) Liver, inhibiting new glucose formation from non-nitrogenous residues.

(iii) Tissues, inhibiting carbohydrate utilization.

It will thus be seen that carbohydrate metabolism is an extremely complex process. Five endocrine glands and the liver are actively concerned in the cycle, and it may be that the effects of prolonged hypoglycaemia upon the endocrine glands in particular impair their efficiency even after glucose has again been administered, and account for the derangement of carbohydrate metabolism which has been found in post-hypoglycaemic coma.

As in the review of the pathological changes during post-hypoglycaemia, the physiological changes will be described under the headings of the tissue constituents and processes affected.

(A) *Cerebral Metabolism.*

(1) *Oxygen Uptake of the Brain.*

It is known that the brain utilizes only carbohydrate in its metabolism, and that its respiratory quotient is consequently 1·0. Himwich and his associates [Himwich, Bowman, Wortis and Fazekas (1937, 1939*a* and 1939*b*) ; Himwich and Fazekas (1937*a*, 1937*b*) ; Himwich, Frostig, Fazekas and Hadidian (1939) ; Himwich, Frostig, Fazekas, Hoagland and Hadidian, (1939) ; Himwich, Martin, Alexander and Fazekas (1939) ; Himwich, Hadidian, Fazekas and Hoagland (1939) ; Wortis, Bowman, Fazekas and Himwich (1941)] have investigated cerebral metabolism during hypoglycaemia by comparing the differences between the blood in the internal carotid artery and that in the internal jugular vein. A detailed analysis of these authors' work cannot be attempted here, but in general it may be said that their results confirm the observations of Damashek, Myerson and Stephenson (1935), who found a diminished utilization of both glucose and oxygen during hypoglycaemia. Himwich and his co-workers conclude that the inability of the brain to utilize the oxygen supplied to it as evidenced by the reduced arteriovenous difference is due to the deprivation of the substrate glucose owing to the low blood sugar, so that the condition is not a true anoxaemia. There is sufficient oxygen available in the arterial blood, but the glucose-depleted brain cells are unable to utilize it. Himwich holds that in severe hypoglycaemia such as is met with in Sakel's treatment, even the intrinsic glucose of the brain cells is used up, and this may account for the irreversible changes which occur in prolonged coma. The work of those authors is an extension of that of Olmsted and Taylor (1924), who, however, ascribed their results to anoxaemia, and has been confirmed by Loman (1940, 1941), Rosenberg (1939) and Wortis and Goldfarb (1940*a*, 1940*b*, 1942).

It is possible that the diminished utilization of oxygen might be counteracted by an increased blood flow, but Leibel and Hall (1938), Lennox and Gibbs (1932), Gibbs, Gibbs and Lennox (1935) and Lennox, Gibbs and Gibbs (1938) could find no evidence of any increase in the blood flow. Yesinick

and Gellhorn (1939–40), Gellhorn (1938), Gellhorn, Darrow and Yesinick (1939), Gellhorn, Ingraham and Moldawsky (1938*a*, 1938*b*), Yesinick and Gellhorn (1939–40) and Gellhorn, Packer and Feldman (1940), working on the association between hypoglycaemia and anoxaemia, found that hypoglycaemia potentiates the increased blood pressure response to intracranial pressure, which if the intracranial pressure were raised in the hypoglycaemia of Sakel's treatment, would cause a greater flow to the brain. As has already been seen, however, the intracranial pressure is not so raised, so that the brain does not receive any extra blood for this reason. It therefore appears that as far as the brain is concerned, one of the main effects of hypoglycaemia is to deprive the neurones of their glucose, without which they cannot utilize the available oxygen. It is interesting to note in this connection that Holmes (1930) pointed out that the dependence of the neurones upon glucose for oxidation is far greater than that of other parts of the nervous system, such as the white matter.

It is interesting to speculate whether this state of " aglucia " of the brain cells is primary to the numerous other changes, such as electrolytic changes, seen in the body in hypoglycaemia, whether the electrolytic changes are not due to the effect of the hypoglycaemia on some other organ such as the suprarenal cortex, and whether it is the aglucia or the electrolytic changes which prevent the cerebral metabolism from returning to normal in prolonged coma.

(2) *Mineral Content of the Brain.*

Liebert and Heilbrunn (1940) studied microincinerated sections of the brains of rabbits who had been treated with insulin along the lines of Sakel's treatment, and found that, while there was no change in the total ash content of the brain, marked changes occurred in the ganglion cells in the form of dust formation, hypomineralization, vacuolation, or complete demineralization. The changes were especially prominent in the cells of Ammon's horn. There was an increase in the mineral content of the glial tissue. Biopsy showed that these changes were present after an insulin convulsion, but became reversed after a certain time.

Yannet (1939), experimenting on cats, concluded that hypoglycaemia caused a shift of potassium from the cell to the extracellular tissues accompanied by a marked shift of intracellular water, and suggested that the osmotic equilibrium is maintained under these conditions by a transfer of sodium across the cell membrane.

(3) *Water Content of the Brain.*

As mentioned above, Yannet (1939) found that water passed from the interior of the cell to the extra-cellular spaces in hypoglycaemia but later returned as sodium permeated into the cell. He was unable to find any changes in the total water of the brain. This conclusion was also reached by Hall (1938) from experiments conducted by Sniffen and Irwin.

(4) *pH of Brain.*

This has been studied by Marshall, McCullock and Nims (1939), who found that the pH of cerebral cortex remained unchanged for from 60–90 minutes

following the injection of insulin, after which it underwent a series of striking fluctuations, consisting of an abrupt rise followed by a slower fall. These fluctuations recurred at short intervals, and in the intervening periods the pH was relatively constant. No corresponding changes in the pH of the blood could be found, and as the chemistry of the changes is unknown the authors could offer no explanation for them.

(5) *Permeability of Brain Cells.*

Spiegel and Spiegel-Adolph (1939) found a marked increase in the permeability of the walls of the brain cells, and that in general the change was proportional to the duration of hypoglycaemia. This increased permeability of the cell wall helps to explain the movements of electrolytes to and from the cell, and as the authors point out, "repeated injuries of the cell membrane may eventually result in more severe lesions of the cells, as shown by the histological examination after prolonged convulsion treatment."

(B) *Changes in the Blood.*

The changes in the constituents of the blood during hypoglycaemia have been reviewed by Katzenelbogen (1940), whose findings may be summarized as follows: There is, of course, the fall in the blood sugar to which further reference is unnecessary. The levels of potassium, urea-nitrogen and amino-acids fall steadily throughout the period of hypoglycaemia, while that of inorganic phosphorus falls for the first 2 hours and then rises; calcium and magnesium appear to be unaffected, while there is conflicting evidence as to the behaviour of the sodium and chlorides.

(C) *Changes in the Cerebrospinal Fluid.*

The cerebrospinal-fluid sugar follows, but lags considerably behind the blood sugar [Day and Niver (1937); Day, Niver and Greenberg (1938)]. After interruption of the hypoglycaemia with glucose, the C.S.F. sugar lags behind the blood sugar in its return to normal, so that the patients' return to consciousness may be associated with a more or less marked hypoglycorrhacia.

(D) *Electroencephalographic Changes.*

Himwich, Frostig, Fazekas, Hoagland and Hadidian (1939) and Himwich, Hadidian, Fazekas and Hoagland (1939) found that there was a direct relationship between the frequency of the alpha waves and the cerebral oxygen consumption, both declining during hypoglycaemia and increasing after the administration of glucose. The delta index displays an inverse relationship, and becomes augmented during the period of diminished oxygen utilization of the brain. This work has been confirmed, *inter alia*, by Gibbs, Williams and Gibbs (1940).

(E) *Changes in Other Organs.*

These changes have already been considered in the section on the pathology of post-hypoglycaemic coma. They have been studied by Tannenberg (1939), whose work has been confirmed by other authors. Tannenberg found that insulin given to rabbits along the lines of Sakel's treatment produced :

(1) *In the heart and skeletal muscles*—definite hydropic changes. The posterior wall of the left ventricle and its papillary muscles were the site of election in the heart, as were the iliopsoas and thigh muscles among the skeletal muscles. The changes consisted of broken muscle fibres of all stages. Most of the changes were considered reversible, but small areas of necrotic cardiac cells were found.

(2) In the *liver* two types of reaction were found :

(*a*) Where the liver was able to release all the glycogen synthesized from various sources before and after the administration of insulin the fall in the blood sugar was not very marked, and damage to vital organs did not result.

(*b*) Where the liver retained the available carbohydrate as glycogen and locked it up, particularly in the centres of the lobules, which became overladen, with constriction of the capillaries, the blood sugar fell to low levels and the heart and musculature showed severe damage. Small areas of necrosis in the liver were observed especially in rabbits treated with high doses of insulin. Terron and Malesani (1939), using the Weltmann and Taka-Ara reactions, were unable to detect any dysfunction of the liver, but in view of the unreliability of liver function tests, Tannenberg's results would seem to be more accurate.

(3) As mentioned earlier, a number of authors have found changes in the cortex of the suprarenal gland which are of interest in view of the ionic changes found in hypoglycaemia, and the probable part which the adrenal cortex plays in the control of ionic changes in the tissues.

From the above summary it will be seen that the only factors which emerge from a study of the physiological changes in hypoglycaemia and which may help in the search for the cause of prolonged coma are :

(1) There is a marked reduction in cerebral metabolism owing to the depletion of the substrate glucose, and, since the brain can only use carbohydrate in its metabolism, prolonged deprivation of glucose may lead to irreversible changes in the cerebral neurones for one of two reasons :

(*a*) Irreversible changes within the neurones themselves.

(*b*) Damage to a part of the carbohydrate controlling mechanism, such as the pituitary gland, sympathetic nervous system, adrenal glands, etc., so that the cerebral neurones are unable to utilize the carbohydrate available in the blood stream after the administration of glucose.

(2) There is a shift of potassium and other electrolytes from the cerebral neurones into the intracellular spaces and glial tissues. A point may be reached

at which these ionic changes become irreversible for one of two reasons similar to those by which the cells cannot utilize their available glucose :

(*a*) The intracellular ionic changes may have resulted in irreversible changes in the structure of the cell as far as the electrolytes are concerned.

(*b*) The mechanism controlling the ionic balance of the body (e.g. adrenal cortex) may be damaged, so that the ionic intracellular arrangements cannot return to normal.

Until more is known of the nature, site and cause of the irreversible changes which accompany prolonged hypoglycaemia, the exact cause of prolonged coma will continue to elude us.

IX. Symptomatology of Post-Hypoglycaemic Coma.

The description of the symptoms of prolonged coma is made more difficult by the varying degrees of severity of the condition which may be encountered. In mild cases, as Case 2 reported above, the patient merely remains unconscious, no symptoms indicative of focal involvement of the nervous system develop, the temperature is only moderately raised, the general condition remains good, and in a matter of hours or days the patient regains consciousness, and in a comparatively short period shows no signs of mental enfeeblement as the results of his experience.

In more severe cases the picture is different. The temperature is raised considerably, up to 105° F., the pulse varies from 110–160 per minute, and the respiration rate is usually 30–40 per minute. The patient is deeply unconscious. Babinski plantar responses may be present for some hours, but the corneal reflex can usually be elicited. A characteristic feature during the first 24-48 hours of severe prolonged coma is the intense myotonic-clonic spasms, which, beginning gradually, become more and more intense until the patient may assume a position of almost complete opisthotonos. These spasms last about 10 minutes and may recur every 10–15 minutes unless they are controlled by intravenous barbiturate or rebreathing. The patient is doubly incontinent, perspires and salivates freely and may vomit any food given by nasal or oesophageal tube. Gradually, again in a matter of hours or days, the myotonic spasms cease, the Babinski responses disappear, the temperature falls, and the patient slowly regains consciousness, and as he does so various signs and symptoms indicating focal lesions of the brain may become apparent. There may be Jacksonian fits (Wortis and Lambert, 1939), spastic deviation of the head and eyes (Scherb and Stone, 1938), hemiplegias (Read, Heilbrunn and Liebert, 1939), paralysis of the ocular muscles (von Pap, 1937), chewing movements (Kant, 1940), facial paralysis (Binzley and Anderson, 1938). The patient's speech is at first dysarthric and aphasic, but gradually returns to normal. His movements in general are clumsy and unco-ordinated and he walks on a broad base. As his condition improves, memory defects of an organic kind are frequently seen. The commonest of these is Korsakov's syndrome, reported by Milch and Bolles (1938), Horwitz, Blalock and Harris (1938) and Billig and Sullivan (1942) amongst other authors. Other memory defects which may occur are retention defects as reported by Kant (1940),

whose patient was able to remember remote events but not recent ones, and misidentification of persons (Horwitz, Blalock and Harris, 1938). The rate of improvement depends upon the severity of the prolonged coma, and it may be days, weeks or months before the patient regains his precomatose level. Some, as will be seen, never reach it.

X. Prognosis of Post-hypoglycaemic Coma.

Prolonged coma may end in (1) death, (2) physical recovery with improvement in original psychosis, (3) physical recovery without improvement in the original psychosis, (4) physical recovery with varying degrees of dementia.

The mortality rate in post-hypoglycaemic coma varies within fairly wide limits. Lester (1938–39) had a mortality rate of 16 per cent. in 25 patients, Rivers and Rome (1944) one of 5 per cent. in 51 cases; Goldman (1940), however, had no fatalities among his 23 cases.

Death usually occurs either from supervening pneumonia or from myocardial collapse. The latter is the commonest cause of death, and is probably due to the fact that the myocardium has already been damaged by the hypoglycaemia intentionally induced.

A number of authors, e.g. Rossman and Cline (1937–38), Lester (1938–39), McKendree (1938), Katzenelbogen (1939), Coyne (1940), James, Freudenberg and Cannon (1938), have reported cases which improved very considerably following the development of prolonged coma, and following his own similar experience Kraulis (1937, 1938) produced protracted comas of up to 12 hours' duration, with a view to increasing the effectiveness of Sakel's treatment. Following up Kraulis' work, Billig and Sullivan (1942) and Wortis, Terris and Korr (1942) have intentionally produced prolonged comas, with, they claim, satisfactory results. These comas are, however, not the same as the post-hypoglycaemic comas now being studied, as the patient is given small amounts of glucose periodically during the coma to prevent the hypoglycaemic state from becoming too profound.

As compared with the above, several authors, e.g. Horwitz, Blalock and Harris (1938), Binzley and Anderson (1938) have reported cases in which no improvement in the patient's psychosis occurred after the post-hypoglycaemic coma, and unfortunately there are many cases reported in which the patient's last condition was worse than his first. The likelihood of any patient improving psychiatrically as a result of post-hypoglycaemic coma is too uncertain to justify its induction for therapeutic reasons.

XI. The Treatment of Post-hypoglycaemic Coma.

The widely varying methods of treatment which have been adopted in cases of prolonged coma indicate that a specific remedy for the condition has yet to be found. This is to be expected, since the actual cause of the condition is, as has been shown earlier, still unknown. If it be assumed that the irreversible changes in the neurones of the brain are the primary cause, the exact nature of those irreversible changes is not known. In the absence of fuller

knowledge of such changes, it is difficult to suggest ways by which they can be influenced. Most authors have approached the problem from a chemical point of view, stressing the part played by glucose in brain metabolism, yet the changes may well be essentially physical and not chemical in nature, and their irreversible character may disappear if the physical milieu of the cells could be changed. If, on the other hand, it is assumed that prolonged coma is essentially due to a breakdown of carbohydrate metabolism, as suggested by the work of Proctor and Easton (1942), the exact point of this breakdown in the cycle of carbohydrate metabolism is unknown, and until it is, a specific remedy for prolonged coma will probably not be found. At present, therefore, treatment for post-hypoglycaemic coma must necessarily be symptomatic—a view insufficiently stressed by most authors.

The forms of treatment which have been tried may be classified as follows :

(1) *Replacement of Tissue-deficiencies.*
   (*a*) Vitamin B_1. (*b*) Nicotinic acid and riboflavine. (*c*) Adrenal cortex hormone. (*d*) Calcium salts. (*e*) Potassium salts. (*f*) Blood transfusion. (*g*) Pitruitrin. (*h*) Insulin.

(2) *Maintenance of the Circulation.*
   (*a*) Administration of fluids. (*b*) Cardiac stimulants. (*c*) Blood-letting. (*d*) Blood transfusion.

(3) *Maintenance of Respiration.*
   (*a*) Oxygen and carbon dioxide. (*b*) Respiratory stimulants.

(4) *Administration of Insulin-antagonistic Substances.*
   (*a*) Adrenaline.

(5) *Lumbar Puncture.*

(6) *Administration of Sedatives.*

(7) *Miscellaneous Forms of Treatment.*

These methods of treatment will now be considered.

(1) *Replacement of Tissue-deficiencies.*

(a) *Vitamin B_1.*—Freudenberg (1937) first asserted that vitamin B_1 was of value in cases of prolonged coma ; his experience was that patients who did not respond to oral glucose promptly awoke on the administration of 2·5 mgm. of thiamine chloride. It is known that in the brains of pigeons with B_1 avitaminosis, pyruvic acid and methyl glyoxal are present. Neither of these metabolites is present in normal brain, and they disappear from the avitaminotic specimens when vitamin B_1 is added. They are similarly present in muscle after hyperinsulinism, so that there would appear to be theoretical justification for Freudenberg's findings, especially as the large amount of carbohydrate usually found in the diet of patients on Sakel's treatment may cause a relative deficiency of vitamin B_1 (Goldfarb and Bowman, 1941). Himwich, Spies, Fazekas and Nesin (1940) found a reduction in the arteriovenous oxygen difference in pellagrous patients similar to that found in the milder stages of hypoglycaemia. Later authors, however, in general have failed to confirm Freudenberg's results. Akos (1939) claimed that the previous

administration of vitamin B_1 reduced the amount of restlessness during coma, but this could only be partially confirmed by Somerfeld-Ziskind *et al.* (1942). Rossman and Cline (1937–38) and Finiefs (1938*a*) recommend the use of vitamin B_1 in prolonged coma, but Wortis and Lambert (1939), O'Neill (1938), Cleckley and Templeton (1941), Gillman and Parfitt (1938), Ribeiro and di Lascio (1939), Freed and Saxe (1939), Rivers (1941) and the present author found that it did not affect the progress of the coma. Somerfeld-Ziskind *et al.* (1942), using the vitamin orally, intramuscularly and intravenously, found that it did not affect the "arousal from coma" times of 27 patients compared with a control series.

In view of these findings it must be concluded that vitamin B_1 has no specific effect in prolonged coma.

(b) *Nicotinic acid and riboflavin.*—Cleckley and Templeton (1941) gave 150 mgm. nicotinic acid and 15 mgm. riboflavin without apparent effect.

(c) *Adrenal cortex hormone.*—Goldman (1940) found that adrenal cortex hormone (cortin) had a marked quietening effect on two of his cases, but the fact that it was given in one case daily for 10 days indicates that it had no specific effect. The part played by the adrenal cortex in carbohydrate metabolism is a complicated one, and a number of substances have been isolated from it which have varying effects. One substance acts like insulin in promoting glycogen formation in the liver [Samson Wright (1945)], but another [Seyley and Dosne (1939)] counteracts the changes in the blood sugar induced by insulin. Seyley and Dosne believe it has a *stabilizing* effect on the blood sugar, and so might be useful in controlling the fluctuating blood sugar found in prolonged coma. Another action of the adrenal cortex is to stabilize the ionic conditions of the tissues which are disturbed in post-hypoglycaemic coma (Rivers and Rome, 1944). There are, therefore, theoretical grounds for believing that adrenal cortex extracts might be of value in prolonged coma, and a further trial of them would be justified now that stronger extracts of more definite composition are available.

(d) *Calcium salts.*—Calcium salts, usually the chloride, have been given to counteract the alkalosis found in post-hypoglycaemic coma, and are recommened by Finiefs (1938*b*), Murphy (1939), James, Freudenberg and Cannon (1938), and Goldman (1940). Gillman and Parfitt (1938), however, found them to be useless.

(e) *Potassium salts.*—Cleckley and Templeton (1941) gave 2 gm. of potassium chloride in 500 c.c. of saline subcutaneously and found that the convulsions ceased after 30 minutes. Skaug and Hellem (1939), however, found in a case of prolonged coma that the blood potassium was higher than normal, although they found that patients with a "long arousal time" after oral glucose quickly responded to the administration of 0·2 per cent. NaH_2PO_4. They maintain that this enables the sugar to be absorbed from the intestine.

(f) *Blood transfusion.*—Reports on the immediate effect of blood transfusion are not available, but Kubo (1937) states that it saved the patient's life in two of his cases, while Wortis and Lambert (1939) were able to treat the condition with "apparent success" by this means, and James, Freudenberg and Cannon believe it to be "of the utmost value." Wortis, Shaskan, Impastato

and Almansi (1941) believe that whole blood contains enzymic factors (other than glucose) essential to brain metabolism. In the present author's experience these claims have not been confirmed, and any beneficial results following blood transfusion have probably been due to the support given to the circulation by the administration of a large quantity of fluid. A female patient, who went into prolonged coma following intravenous insulin, strikes a warning note [Spencer (1947)]. Although the bloods were cross-matched microscopically to ensure compatibility, a violent rigor followed by a severe degree of cardiac failure occurred. It is probable that the patient, a multipara, was an Rh-negative subject who was transfused with Rh-positive blood. The patient recovered as her general condition was good when the transfusion was started. Had the general condition been poor, as it frequently is when such patients are transfused, the outcome would probably have been fatal. As a precautionary step all patients undergoing Sakel's treatment should have their blood grouped before treatment commences, and the blood-grouping should include the Rh factor.

(g) *Pituitrin.*—Gillman and Parfitt (1938) gave pituitrin (0·5 c.c.), but it does not appear to have influenced the course of the patient's coma.

(h) *Insulin.*—It is interesting to note that some authors [Molony and Honan (1937), Easton (1938), Ribeiro and di Lascio (1939), O'Neill (1938)] have given further insulin (10–30 units) during prolonged coma in view of the high blood-sugar values obtained. There appears to be no justification for such a step since, as Proctor and Easton (1942) have shown, the blood sugar is probably not consistently high, but fluctuates a great deal. This is probably due to a derangement of the carbohydrate metabolism, as the quantities of glucose usually injected in post-hypoglycaemic coma actually represent quite a small carbohydrate intake, and to inject further insulin probably only serves to delay the stabilization of the carbohydrate metabolism still further.

(2) *Maintenance of the Circulation.*

(a) *Administration of fluids.*—Two schools of opinion exist as to the advisability of giving fluids in cases of prolonged coma. The one advocates giving adequate fluids in order to support the circulation in view of the large amount of fluid lost in the profuse perspiration [Fraser and Sargant (1940), Timmer (1938), Theato (1939), Finiefs (1938*a*), O'Neill (1938)]. As has been shown in the section on morbid anatomy, the heart itself is affected by hypoglycaemia and every care must be taken to maintain the circulation, as the commonest immediate cause of death in prolonged coma is either terminal pneumonia or myocardial failure. Intravenous saline can be of much value in this condition, but it needs to be administered with considerable caution since, as in cases of ordinary diabetic coma, it is possible to overload the heart if too much fluid is given by this route, especially if it be given too quickly. Estimations of blood volume are useful, but in general it may be said that isotonic saline through a stomach tube is safer from a cardiac aspect than large quantities intravenously.

Other authors following O'Neill (1938) have sought to promote dehydration

instead of administering fluids to counteract the dehydration already existing. Rivers (1941) and Rivers and Rome (1944) used solutions of sodium arabinate, dextrosorbitol, mannitol, styracital and concentrated lyophile serum for this purpose. They claim that "in all instances" clinical improvement was obtained within the hour. The administration of dehydrating substances is based on the presence of intracellular oedema of the brain cells, since at post-mortem many of the cells are found in a swollen condition, and Rivers and Rome hold that as a result of ionic changes there has been a passage of water into the cell which is reversed by the giving of dehydrating substances. Whether such a reversal in the absence of the correction of the ionic imbalance is desirable is open to doubt, as the intracellular oedema may be protective in character. That dehydrated animals do not have convulsions during hypoglycaemia was shown by Drabkin and Ravdin (1930, 1937) but Drabkin and Shilkret (1927–28) found that despite this, dogs which had been given fluids invariably recovered on the administration of glucose, whereas those that had been deprived of water for more than 4 days did not survive. Tyler, Greeley and Drury (1939) found that dehydration also leads to an increase in the basal insulin requirements of the depancreatized dog, which would seem to indicate that dehydration increases the difficulty of stabilizing the carbohydrate metabolism. In the absence of fuller clinical details about Rivers and Rome's (1944) patients, it is difficult to assess the efficacy of their dehydrating methods, and until more conclusive evidence of the value of dehydration is obtained it would seem advisable to continue to give adequate amounts of fluids.

(b) *Cardiac stimulants.*—Theato (1939) regarded coramine as the "chosen remedy" for prolonged coma, giving it in the very large doses of 77 gm. in 12 hours, of which 55 gm. were given in 2 hours. Other authors, e.g. Rossman and Cline (1937–38), Gillman and Parfitt (1938) and Easton (1938) have given it in more usual doses with beneficial effect on the cardiovascular and respiratory systems. While it probably does not, as Theato claimed, have a specific action on the myotonic spasms, it is undoubtedly useful in maintaining the circulation. Other cardiac stimulants which have been used by various authors are: caffeine sodium benzoate [Easton (1939), Wortis, Bowman *et al.* (1937), O'Neill (1938)], camphor and sympatol [Theato (1939)], strychnine [Molony and Honan (1937), McKendree (1938)], digitalis [Easton (1939), Murphy (1939), Lester (1938–39), O'Neill (1938)], and cardiazol [Lester, (1938–39)], but none appear to have any effect other than that of supporting the circulation.

(c) *Blood-letting.*—Theato (1939) also recommended the withdrawal of 200 c.c. of blood as a means of supporting the circulation. This would probably prove useful in those cases in which signs of pulmonary oedema indicate the onset of right-sided heart failure.

(d) *Blood transfusion.*—This is a valuable means of supporting the circulation, and has already been considered under a previous heading.

(3) *Maintenance of Respiration.*

(a) *Oxygen and carbon dioxide.*—Continuous inhalation of oxygen and 5 per cent. carbon dioxide through a nasal catheter is most useful, and may tide the

patient over what would otherwise have been a fatal phase. Its use is reported by Gillman and Parfitt (1938), Strecker (1938), Kant (1940) and Finiefs (1938*a*). The use of higher concentrations of carbon dioxide or of a rebreathing bag (Goldman, 1940) is useful in cutting short the myotonic spasms if these have been allowed to develop.

(b) *Respiratory stimulants.*—Lester (1938–39) used lobeline to stimulate the respiration, while a large number of authors have given atropine, e.g. McKendree (1938), Wortis, Bowman *et al.* (1937), Goldman (1940), Cleckley and Templeton (1941) and Proctor and Easton (1944). It is certainly most useful when early signs of pulmonary oedema are developing, and in addition to the effect upon the respiration, it reduces the amount of salivation and so minimizes the loss of fluids from the tissue.

(4) *Administration of Insulin-antagonistic Substances.*

(a) *Adrenaline.*—In the early years of Sakel's treatment adrenaline was given almost as a routine in cases of post-hypoglycaemic coma, because of the fact that if equivalent doses of adrenaline and insulin are given intravenously the fall in the blood sugar which would normally follow the injection of the insulin can be entirely neutralized. Strecker (1938), however, found that the administration of adrenaline in prolonged coma increased the incidence of convulsions, a finding confirmed by Horwitz, Blalock and Harris (1938), while Binzley and Anderson (1938) regard its use as undesirable " as it accelerates the rate of an already overworked heart, and any liver glycogen mobilized will be unnecessary because the blood sugar is already normal or above." Wortis, Bowman *et al.* (1937) found that the colour of a patient improved following the injection of 5 minims of adrenaline, but in general, the results of its use have not justified the risk of inducing further convulsions, and the drug would seem to have no place in the treatment of prolonged coma.

(5) *Lumbar Puncture.*

In view of the fact, noticed in a previous section, that the pressure of the cerebrospinal fluid is normal or only slightly raised in post-hypoglycaemic coma, it would appear that lumbar puncture with withdrawal of C.S.F. would not be helpful in the condition. Katzenelbogen (1939), Kant (1940) and Finiefs (1938) amongst others, however, found that it relieved the patients' restlessness, but Fraser and Sargant (1940) were not convinced of its usefulness.

(6) *Administration of Sedatives.*

Patients who die in prolonged coma do so either from exhaustion with myocardial failure or from an added infection such as pneumonia. The severe, generalized myotonic spasms, so frequently found as part of the syndrome, are extremely exhausting and should be controlled as completely as possible. A number of sedatives, e.g. alcohol intravenously [Abely and Feuillet (1941)], paraldehyde [Lester (1938–39)], morphine [Rossman and Cline (1937–38)], and luminal [Theato (1939)], have been given with a view to allaying the general restlessness, but the short-acting intravenous barbiturates such as sodium

amytal or hexobarbitone are most valuable in aborting and controlling the severe myotonic spasms. Several authors, e.g. Scherb and Stone (1938), Horwitz, Blalock and Harris (1938) and Wortis and Lambert (1939) refer incidentally to their use, but none lays sufficient emphasis on the vital part they play. Ideally, a patient in prolonged coma should never be allowed to have more than one severe myotonic spasm. An intravenous barbiturate should be given at once. Control of the seizure is immediate, and if 1 gm. of the drug is given slowly so as not to produce anaesthesia no seizure will occur for some time. As soon as the seizures restart further barbiturate should be given, and up to 3 gm. of hexobarbitone may sometimes be required over a period of 8 hours, by which time the myotonic spasms will probably have ceased. That the giving of the barbiturate does not retard the recovery of the cerebral neurones follows from the work of Wortis (1935), who showed that barbituric acid derivatives did not depress the respiratory quotient of brain slices in the Barcroft-Warburg apparatus, i.e. they did not prevent the uptake of oxygen by the brain, so that in prolonged coma they should not prevent the recovering brain cells from utilizing the available oxygen as they become able to do so. Indeed, Hrubetz (1938) and Tyler (1940) have shown that the previous administration of barbiturates can prevent the cerebral damage of hypoglycaemia; they can therefore be given with every confidence in prolonged coma.

(7) *Miscellaneous Adjuncts to Treatment.*

Antipyretic methods such as cold packs and alcoholic sponges have been recommended by O'Neill (1938), and ice enemata and iced water lavage by Goldman (1940). Despite the existing alkalosis, Ribeiro and di Lascio (1939) have given sodium bicarbonate, and also a preparation termed "organo-cardio-renal serum" as well as anti-anaemic liver extract ("campolon"). No benefit appears to have accrued from these measures.

As will be seen from the above account, no specific remedy for prolonged coma is available. Nor is one likely to be found until the precise cause of the condition has been discovered. Until that occurs it is necessary to bear in mind that the adverse effects of hypoglycaemia are systemic in character and are not confined to the nervous system. As Dunner, Ostertag and Thanhauser (1933), Ernstone *et al.* (1935), Jorgensen (1940), Tannenberg (1939) and Terron and Malesani (1939), have shown, other systems, and especially the cardio-vascular system, can be directly damaged by hypoglycaemia. In prolonged coma, therefore, we are probably dealing with a heart which has already been damaged. All that can be attempted is to support the circulation as far as possible, and to lighten the demands made upon it by controlling the restlessness and myotonic spasms by the use of intravenous barbiturates.

XII. Theories of Causation of Post-hypoglycaemic Coma.

The large number of theories which have been advanced to explain the cause of post-hypoglycaemic coma indicates that probably none of them is satisfactory. This is because most of the theories do not deal with the funda-

mental changes which are found in the condition, but content themselves with the discussion of secondary changes which accompany the more fundamental ones. Attention has been devoted too exclusively to the pathological findings in the brain and insufficient attention has been paid to the changes in the other organs; hence the search for the cause of the condition has tended to be limited to the brain, damage to which results in the symptoms of prolonged coma. It is not enough to say that hyperinsulinism causes irreversible changes in the brain; we have to go on to inquire into the causes and nature of these changes, for the cause may not lie in the cells themselves, but in some other organ or organs which control the metabolism of the cells. That is to say, the search for the cause of prolonged coma must be extended to cover the effects of hypoglycaemia in all the tissues of the body, with particular attention being devoted to the organs which play a part in carbohydrate metabolism. It appears that the following facts have not received the emphasis they deserve :

(1) Irreversible changes occur in the cells from prolonged hypoglycaemia, i.e. they cannot be reversed by restoring the blood-sugar level, we need to know the nature of these changes, for it may be possible to affect them in other ways.

(2) These irreversible changes are not restricted to the brain. They occur also in at least the heart (Tannenberg, 1939), the suprarenals (Jansen and Waaler, 1940), and probably the kidneys (MacKeith and Meyer, 1939).

(3) There is a profound disturbance of the ionic balance of the body. This disturbance may itself result in irreversible changes in the cells (Liebert and Heilbrunn, 1940).

(4) There is an equally profound disturbance of the carbohydrate metabolism in prolonged coma (Proctor and Easton, 1942), and it is noteworthy that the improvement in the patient's condition coincides with the return of the carbohydrate metabolism to normal.

These facts indicate that probably the ultimate cause of the post-hypoglycaemic coma is not to be found in the effect of the hypoglycaemia upon what may be called the "terminal" tissues such as the cerebral neurones and myocardial cells, but in its effect upon other tissues which control the metabolism of the "terminal" tissues. Of especial interest in this connection is the effect of hypoglycaemia on the adrenal cortex, the pituitary gland and the sympathetic nervous system, all of which are known to play a part in the cycle of carbohydrate metabolism.

The various theories which have been advanced to explain post-hypoglycaemic coma will now be briefly reviewed in the light of the above remarks, and therefore, with the proviso that most of them are concerned with changes which accompany prolonged coma rather than with its cause.

(1) *The Vascular Theory.*
(2) *The Anoxic Theory.*
(3) *The Toxic-metabolism Theory.*
(4) *The Oxyachrestic or Aglucic Theory.*

These theories have already been examined in Section VII above.

(5) *The Autonomic Imbalance Theory.*

A great deal of work has been done on the behaviour of the autonomic nervous system during hypoglycaemia. Parker (1940) holds that both the sympathetic and parasympathetic divisions are stimulated, while Wespi (1938) believes that "the autonomic response to insulin may vary from day to day in one and the same patient." These changes are probably brought about by the action of insulin on the hypothalamus, and if they become too severe, the cells of the hypothalamus undergo irreversible changes which result in prolonged coma.

(6) *The Increased Combustion of Protein Theory.*

Wortis and Lambert (1939) believe that certain of the manifestations of prolonged coma, such as the fever, can be attributed to an increased combustion of protein in the presence of impaired carbohydrate metabolism. It is difficult to see how this can happen in the case of the nervous system, which can use only carbohydrate in its metabolism.

(7) *The Deficiency of Tissue-essentials Theory.*

This holds that the condition is due to a tissue-deficiency of such essential substances in carbohydrate metabolism as vitamin B_1. The fact that patients developing prolonged coma do not apparently suffer from such deficiencies, that prolonged coma may not develop until the patient has already had many normal comas, and the absence of any response to vitamin B when the condition does occur are sufficient evidence against the theory.

Other theories, such as the too rapid increase in dosage, too profound or too prolonged coma, while of undoubted aetiological significance are not true theories as to the *cause* of prolonged coma, and they have already been considered in Subsection VI on aetiology.

Conclusions.

Summing up, it may be said that the cause of post-hypoglycaemic coma remains unknown, and will probably remain so until a great deal more is known about cellular respiration and the effect of hypoglycaemia upon it. All that is known at present are certain aetiological factors which influence the incidence of post-hypoglycaemic coma. These factors are :

(1) That the majority of prolonged comas occur in the first 14 days of treatment.

(2) That the *depth* of coma is important. If the duration of hypoglycaemia is kept constant, the more profound the hypoglycaemia becomes the greater the possibility of prolonged coma developing.

(3) That the *duration* of hypoglycaemia is important. Cases 1 and 2 reported in subsection V prove that even comparatively light stages of hypoglycaemia, if sufficiently prolonged, can result in prolonged coma.

(4) The prevention of prolonged coma is directly related to the skill and experience of the therapist. Post-coma confusion is a warning sign that the patient may develop prolonged coma on the following day, and patients developing such confusion should be given a few days'

rest from treatment. Patients on hypoglycaemic treatment should be given fully adequate diets, including more than ordinarily sufficient amounts of vitamin B, as a relative deficiency of this vitamin may easily occur. This is the more important, as the increase in weight which usually accompanies the treatment may mask the presence of nutritional deficiencies.

Summary.

This paper deals with the nervous complications of Sakel's treatment. The most important of these is post-hypoglycaemic coma. Two examples of this condition which followed light coma of long duration are described, and the aetiology, pathology, physiology, symptomatology, prognosis, treatment and theories of causation of the condition are discussed.

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POSTERIOR CUTS IN PREFRONTAL LEUCOTOMY: A CLINICO-PATHOLOGICAL STUDY.

By Alfred Meyer, M.D., and Turner McLardy, *M.B.E.*, B.Sc., M.B., Ch.B., D.P.M.

From the Department of Neuropathology, Research Laboratory, Maudsley Hospital, London.

The usual leucotomy cut in this country, made through burr holes orientated by means of skull measurements, in the majority of cases enters the brain at about the middle of pars triangularis of the inferior frontal gyrus (Brodmann's Area 45), and if performed in a strictly coronal plane remains entirely within the prefrontal region. Intentionally or unintentionally cuts are not infrequently placed either anterior or posterior to this plane. That cuts made posterior to strictly prefrontal levels are often followed by an unfavourable post-operative course distinguished by particularly severe personality change, persisting incontinence, vasomotor, trophic and neurological disturbances has been demonstrated by Knight (1943), Meyer and Beck (1945), Ziegler and Osgood (1945), Reitman (1946) and others.

Such posterior cuts usually involve the posterior orbital region, the striatum, the external capsule or the premotor region. Of these, the posterior orbital region has recently received special attention, particularly in American experimental work. It had long been known that after bilateral frontal lobectomy hypermotility might develop in monkeys, but it was left to Ruch and Shenkin (1943) to show that this occurred only when Area 13 of the posterior orbital region (delineated in the monkey's brain by Walker in 1940) was included in the lesions. This was confirmed by Fulton (1947) in monkeys, but not in a chimpanzee.* Richter and Hines (1938) and Mettler (1945), on the other hand, concluded that to produce spontaneous hyperactivity in monkeys the striatum in addition must be damaged.

Smith (1938) and Bailey and Sweet (1940) observed inhibition of respiration and gastric peristalsis after stimulation of a region roughly comparable to Area 13 in various species of animals, and Bailey and Bremer (1938) obtained abnormal electroencephalographic potentials from the same region in the cat upon stimulating the central end of the cut vagus nerve. Some of these findings have been confirmed, and amplified, by Delgado, Fulton and Livingstone (1947).

In view of these experimental results we have paid special attention to the posterior orbital region in the following analysis of the clinical and pathological data from our leucotomy material. It should be borne in mind, however,

* Fulton, in lectures in this country, recently described further interesting findings after electrical stimulation of the posterior orbital region in chimpanzees and man, but they have not yet been published and will not therefore be quoted in this paper.

that in leucotomy the lesions are much less precise in their location than in cortical stimulation or ablation. For instance, a leucotomy cut which involves the head of the caudate nucleus is very likely at the same time to damage the premotor region or the posterior orbital region, either directly, or more remotely by severing their afferent and efferent fibres where they course out of and into the internal capsule. This imposes the need for particular care in the evaluation of our findings, and deters us from any too strict a statistical treatment of our tabulated data. Another limiting factor in our data is that in none of our cases had a scientific attempt been made to record the relevant symptoms before or after the operation. We are, thus, not in a position to make any statement on important indications of autonomic function, such as blood pressure, respiration, heat regulation, pupillary reaction, gastric motility, sweating, salivation, pilo-motor reaction, electrical skin resistance and psychogalvanic reflex. We have had to confine ourselves to some gross autonomic and other signs which we could be reasonably certain would not have been overlooked in the usual routine investigation. This, again, necessitates the greatest reserve in analysis and conclusions.

Out of a total of 60 leucotomy cases 40 were suitable for clinico-pathological study. Twenty-two were found to have in both hemispheres what in this paper will be called " posterior " cuts, i.e. they had involvement of the posterior half of the orbital region, the striatum, the premotor region (Areas 6 and 44 of Brodmann), the region of the external capsule (insular cortex, claustrum, capsula externa or extrema), or any combination of these. These 22 cases have been collected together in Table I. The regions involved in each case are indicated by plus signs within the appropriate columns, except in the case of the posterior orbital region, where further subdivision has been carried out into terms of involvement of medial, central and lateral thirds—this because Area 13 has not yet been defined in the human brain. In addition to columns for these four posterior regions we have included one for indication of involvement of the anterior half of the orbital region, for reasons to be mentioned. Other segments of the prefrontal region have been omitted, since they are not very relevant to our main theme.

The remaining 18 cases, that is to say the more truly prefrontal leucotomies, are collected together in Table II, and analysed in terms of involvement of the same regions.

On the right hand-sides of the Tables have been recorded the clinical sequelae reported in each case to have followed the operation. They have been distributed under five headings :

Personality change has been graded according to severity in terms of three degrees of plus, irrespective of whether the change was of the euphoric type or of the akinetic (torpid) type. Where the brevity of post-operative survival limited evaluation of the clinical observations the grading has been bracketed.

General restlessness is often included within the term "personality change," but we have given it separate mention, wherever reported, on account of the experimental evidence described above that its manifestation implies damage to a particular posterior region. It cannot, however, be compared directly with the restless pacing of experimental animals which Ruch and Shenkin

regard as the characteristic result of bilateral damage to Area 13, for all our six patients displaying restlessness were confined to bed.

Vasomotor and trophic lesions.—These terms have been used to cover such symptoms as cyanosis of extremities, oedema and blisters of the skin.

Persisting incontinence of urine was taken to be positive when of over six weeks' duration.

Miscellaneous.—In this column "E" has been used to denote epilepsy developing for the first time after operation; "H" to mark the occurrence of hyperpyrexia as a prominent sequel; "N" to indicate the development of signs of nutritonal deficiency; "R" to denote marked respiratory disturbance; and "U" to indicate the appearance of uraemia. All purely neurological sequelae have been omitted.

The penultimate column shows the post-operative survival period; the last column those cases in which death can be attributed definitely to an intercurrent illness.

In spite of the shortcomings in the clinical data and the other limiting factors mentioned, not a few points of theoretical and practical interest can be derived from the tables.

In the first place, the contrast between the *general total of sequelae* in Tables I and II is most striking: 42 clinical items in the group of cases with posterior cuts, only 8 in the group with essentially prefrontal cuts.

A second striking point is that the *survival period* of the cases with posterior cuts is, on the average, much lower (6½ months) than the average of those in Table II (1½ years), especially if, as has been done in calculating the former average, one takes into account in Table I only the uppermost 17 cases, which had bilateral involvement of either the posterior orbital region or the striatum, or both. A third notable fact is that only one of the top 17 cases in Table I definitely died from an *intercurrent disease*, as against 10 of the 18 cases in Table II. Manifestly, therefore, posterior cuts, especially if they affect the striatum or posterior orbital region, tend to determine relatively early death, i.e. "*delayed post-operative death.*" Many of the "clinical sequelae" reported were undoubtedly either primary or precipitating lethal factors. In this connection it is interesting to recall that Heath, Freedman and Mettler (1947) found that after bilateral enucleation of striatal tissue in felines death always occurred within a few days, due, they thought, to upset of metabolic function.

The *personality change*, it can be seen, tends to be severest when the posterior lesions are most widespread. A mild degree of change was reported in three of the cases with the lesions confined to the prefrontal region, and it can safely be assumed that in other cases in Table II lesser degrees of change passed unrecorded. Hence personality change is not dependent upon, although amplified by, damage to posterior regions of the frontal lobes. This occurrence of personality change after lesions confined to the prefrontal regions proper is stressed (see also Meyer and McLardy, 1947), because it has recently been contended by Hebb (1945) that the personality is not affected by almost total removal of both prefrontal regions. That the personality change becomes more severe in posterior cuts may simply signify that the prefrontal connections have been more completely cut off.

TABLE I.—*Bilateral "Posterior" Cuts.*

Case number.	Regions involved.										Clinical sequelae.					Survival.	Intercurrent cause of death.
	Posterior orbital.		Striatum.		Pre-motor.		Exteral capsule.		Anterior orbital.		Personality change.	General restlessness.	Vasomotor and trophic.	Persisting incontinence.	Miscellaneous.		
	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.							
3	Lat. Cent.	Lat.	+	+	..	.	..	.	..	.	+	..	..	+	N	2 mth.	..
4	..	..	+	+	+	+	+	+	..	.	+++	+	+	+	U/N	4 mth.	..
10	Lat. Cent.	Lat. Cent.	..	.	..	.	..	.	..	.	++	..	+	..	N	3 yr.	..
11	Lat. Cent. Med.	Lat. Cent.	+	+	..	.	..	.	+	.	++	..	..	+	..	5 mth.	..
16	Lat.	Lat.	+	+	..	.	..	.	..	.	+	..	..	..	..	7 wk.	..
20	..	..	+	+	..	.	..	.	..	.	++	..	+	+	..	2¼ yr.	+
22	Lat.		+	+	+	+	+	+	..	.	..	..	+	..	..	9 wk.	..
29	Lat. Cent. Med.	Lat. Cent. Med.	+	+	..	.	..	.	..	.	..	..	..	..	H	9 dy.	..
32	Lat. Cent.	Lat. Cent.	+	+	+	+	+	+	..	.	++	..	+	..	..	7 wk.	..
33	Lat. Cent.	Lat. Cent.	+	.	..	.	..	.	..	.	+++	+	+	+	..	10 wk.	..
38	Lat. Cent.	Lat. Cent.	..	.	..	.	..	+	+	.	+	+	..	+	..	..	1½ yr.
41	Lat. Cent.	Lat. Cent.	..	.	..	.	..	.	..	.	..	..	..	..	H	6 dy.	..
49	Lat.	Cent.	+	.	..	.	..	.	+	.	(++)	+	..	..	H	24 dy.	..
52	Lat.	Lat. Cent.	+	+	+	+	+	.	..	.	(+++)	+	..	..	..	20 dy.	..
56	Lat. Cent. Med.	Cent. Med.	+	+	+	+	+	+	..	.	+++	..	+	+	..	9 mth.	..
58	..	..	+	+	..	.	+	.	..	.	(++)	+	..	..	U	7 dy.	..
59	Lat. Cent.	Lat. Cent.	..	.	..	.	..	.	..	.	..	..	..	..	R	4 hr.	..
26	..	..	..	.	+	+	..	.	..	.	..	..	..	..	E	3¾ yr.	+
8	..	..	..	.	..	.	+	+	..	.	..	..	..	..	..	1¼ yr.	+
27	..	..	+	.	..	.	+	+	..	.	..	..	..	..	..	3¾ yr.	+
37	..	..	+	.	..	.	+	+	..	.	..	..	..	..	..	4¼ yr.	+
47	..	..	..	.	..	.	+	+	..	.	..	..	..	..	..	3½ yr.	+

TABLE II.—*Essentially Pre-frontal Cuts.*

Case number.	Regions involved.										Clinical sequelae.					Survival.	Intercurrent cause of death.
	Posterior orbital.		Striatum.		Pre-motor.		External capsule.		Anterior orbital.		Personality change.	General restlessness.	Vasomotor and trophic.	Persisting incontinence.	Miscellaneous.		
	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.							
5	..	..	..	..	..	..	..	..	+	+	..	..	..	..	E	1½ yr.	..
18	..	..	..	..	..	..	..	..	+	+	+	..	..	..	..	1¼ yr.	+
19	..	..	..	..	..	..	..	..	+	+	+	..	..	..	..	6 mth.	+
34	..	..	..	..	..	..	..	..	+	+	..	..	..	..	..	2 yr.	..
44	..	..	..	..	..	..	..	..	+	+	..	..	..	..	..	3¾ yr.	+
57	..	Med.	..	..	..	..	..	..	+	+	++	..	..	..	..	2½ yr.	+
9	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	1¾ yr.	+
12	..	..	..	..	..	..	..	..	+		..	..	..	+	E	2 yr.	+
13	Lat.		+		..	..	..	..		+	..	..	..	..	N	7 wk.	..
14	..	..	..	..	..	..	..	..	+		..	..	..	..	..	8 mth.	..
21	..	..	..	..	..	..		+		..	..	..	..	..	..	1¾ yr.	..
31	..	..	..	..	..	..	..		..	..	..	..	..	..	..	1¼ yr.	+
35	..	..	..	..	..	..	..		..	..	..	..	..	..	..	1 yr.	..
36	..	..	..	..		+		+	..	..	..	..	..	..	..	2 yr.	..
39	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1 yr.	+
46	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	9 mth.	+
60	..	..		+	..	..	..	..	+		..	..	..	..	..	3 yr.	..
61	Lat.		..		..	..	..	..		+	..	..	..	..	..	1¼ yr.	+

Another conspicuous fact is that all cases displaying *general restlessness*,* all displaying *vasomotor or trophic lesions* and all displaying any of the "miscellaneous" sequelae except epilepsy, fall within the upper 17 cases of Table I, i.e. possess bilateral damage to either the posterior orbital region or the striatum, or both, and often to the premotor region as well. A noteworthy corollary to this is that none of the six cases having bilateral involvement of only the anterior half of the orbital region shows any such sequel, beyond personality change. This would indicate that in man, as in animals, the mechanism concerned in the production of these clinical changes, so far as related to the orbital region, is confined to its posterior half. The central third is, by direct homology, the most likely to correspond to Area 13 of monkeys. Fulton, however, has suggested that perhaps in chimpanzees and man Area 13 is more widespread. Final settlement of the matter will depend upon exact delineation of the area in the human brain by architectonic studies.

It should be mentioned here in passing that although evidence is accumulating that the cingulate region may have important autonomic functions (McCulloch, 1944; Smith, 1945; Kremer, 1947), the involvement of the anterior cingulate region in our material was about equally distributed between cases falling into the top 17 of Table I and those of Table II. Hence damage to this area (Brodmann's Area 24) has apparently no causal connection with at least the rather gross types of clinical manifestations to which our report is limited.

That the four cases having bilateral posterior lesions confined to the external capsule (the bottom group of Table I) display no sequelae whatsoever indicates clearly that the anatomical substrate concerned in these undesirable clinical changes does not include the external capsule, claustrum, extreme capsule or insular cortex (or, it should be added, the uncinate fasciculus, which was bilaterally involved in at least three of these four cases). The other three posterior regions, however, cannot be dealt with in isolation, for lesions in the region of the head of the caudate nucleus are extremely liable to damage fibres there which are projecting to and from premotor or orbital cortex. The four cases of bilateral striatal damage without direct posterior orbital lesion show no significant difference in incidence of general restlessness and vasomotor or trophic lesions from the six with bilateral posterior orbital damage but no striatal involvement. Fulton, Livingstone and Davis (1947) have, in fact, suggested that fibres projecting to Area 13 pass through the caudate nucleus. This would, to some extent at least, reconcile the views of Richter and Hines and Mettler (who relate restlessness to striatal damage), and of Ruch and Shenkin (who relate it to posterior orbital damage).

With regard to vasomotor and trophic disturbances, it will be recalled that Kennard (1935) created vasomotor changes in monkeys by ablation of the premotor area, and that in Ziegler and Osgood's leucotomy cases displaying vasomotor and trophic phenomena there seemed to be some relationship with posterior cuts, as determined by contrast radiography.

Persisting incontinence of urine is a very general symptom which cannot

* In a previous communication (1948) based on a smaller number of cases a more reserved statement was made on this point.

be expected to correlate closely with damage to any circumscribed region, for although it is well known to be brought about by lesions of the dorsal part of the premotor region, it may, on the other hand, be determined simply by the general deterioration in a patient's conduct —and, in fact, all but one (No. 38) of our nine cases exhibiting it either had lesions likely to affect fibres from the dorsal premotor region or showed post-operative mental deterioration.

The "*miscellaneous*" *sequelae* are too few to warrant full discussion at present. It is interesting, however, that of the three cases developing *epilepsy*, the two in which it commenced within a few months had the most anteriorly placed cuts in our series. The third case (No. 26) had posterior cuts, but here the epilepsy bore a somewhat doubtful relationship to the operation (since it did not commence until two years later, and two courses of E.C.T. had been given in the meantime). A fourth case, mentioned in a previous communication (1948), has been omitted from the present series because of the discovery of an independent organic disease of the brain which complicates the picture. A fifth case (not included in the present series) has only just been received which shows the combination again of post-operative epilepsy and an unusually anterior lesion on at least one side. The damaged anterior regions peculiar to these three cases lie definitely rostral to any of the sites which Russell (1947) has tentatively related to post-traumatic epilepsy. They remind one more of Pennybacker's (1945) series of cases of abscess of the anterior pole with epilepsy. Our cases, however, are still too few and incompletely investigated to warrant further discussion at present.

Nutritional deficiency took the form of pellagrous symptoms in two cases, Wernicke syndrome in one case and vitamin C-like deficiency symptoms in a fourth. It is difficult to determine what the causes, extrinsic or intrinsic, of this nutritional deficiency may be in these patients, and in view of the complexity of the whole problem of nutritonal deficiency it would be idle to speculate.

The three cases displaying *hyperpyrexia* revealed no histological evidence of infection of the brain or meninges. They had in common only bilateral damage of the posterior orbital region.

It is difficult to say whether the *uraemia* which developed after operation in Cases 4 and 58 had anything to do with the damage to the brain, but it has been recorded in view of Cumings' (1942) findings in cases of head injury.

The one case of marked *respiratory disturbance* (No. 59) merits special attention in view of the bearing which experimental findings may have in its interpretation. Because the patient was suffering from impetigo of the scalp 100,000 units of pure penicillin were run into each of the leucotomy wounds at the time of operation. The anaesthesia was without incident, but very shortly after recovery from it the patient showed left-sided twitching, and his respiration was noted to have become alarmingly slow and irregular. Artificial respiration and oxygen were administered repeatedly. Twitching continued at intervals. Two hours after the operation the respiratory rate became 30 per minute, and a quarter hour later the patient developed a first major epileptic fit. Fits recurred at 5-minute intervals and were not fully controlled by intramuscular gardenal, being reduced to one per half hour. Respiration

again became irregular but deep, and in spite of further gardenal and coramine injections the patient died during his eleventh fit, four hours after return from the operating theatre. Diagrams 1 and 2 indicate the position and extent of the cuts. The interpretation of the symptoms is not simple, on account of the known epileptogenic effect of penicillin in contact with the C.N.S. (Johnson, Walker, Case and Kollross, 1946). The respiratory effects were so primary—long before major epileptic fits developed—that one is led to postulate a double aetiology for the symptoms, attributing the respiratory disturbance to the bilateral damage of the posterior orbital region, the site of the lesions which Bailey and Sweet and Delgado, Fulton and Livingstone found to produce respiratory inhibition in animals.

That other cases with bilateral involvement of the posterior orbital region did not display such respiratory disturbance—or, for that matter, the fact that all cases with similar lesions did not display identical sequelae—does not necessarily invalidate the positive correlations which have been pointed out. Quite apart from the possibility of constitutional variation in the homeostatic mechanism of different individuals, it may well be that grossly similar lesions differ in details which we have not yet distinguished, but which may determine differences in the nature of the upset of physiological balance. We have, actually, examined other variables than these discussed in this paper—e.g. involvement of the ventricles, damage to fasciculus subcallosus, affection of grey as well as merely white matter of Brodmann areas—but have found no correlation trend.

The anatomical pathways concerned in these post-operative autonomic and other changes remain obscure. Only one of the many postulated cortical connections of the hypothalamus has been definitely established—namely, the connection with the orbital cortex by way of unmyelinated periventricular fibres which relay in the magnocellular part of the dorsomedial nucleus of the thalamus. The present writers, together with E. Beck (1947), previously described some histological evidence that the medial part of the anterior half of the orbital region connects with the anterior part of pars magnocellularis of the dorsomedial nucleus. Further histological investigation is necessary, and is in progress in this laboratory, to determine the precise thalamic, or other, connections of the posterior orbital region.

Summary.

Clinico-pathological analysis is made of 40 cases of prefrontal leucotomy, with particular reference to the relation of restlessness and certain autonomic disturbances to the posterior orbital region. The results emphasize the potentialities of such studies and the importance of full clinical investigation of cases before and after operation and their eventual correlation with the pathological findings.

Acknowledgments.

We wish to acknowledge our gratefulness to all those who contributed the clinical records and brain material utilized in this study, and in particular, to

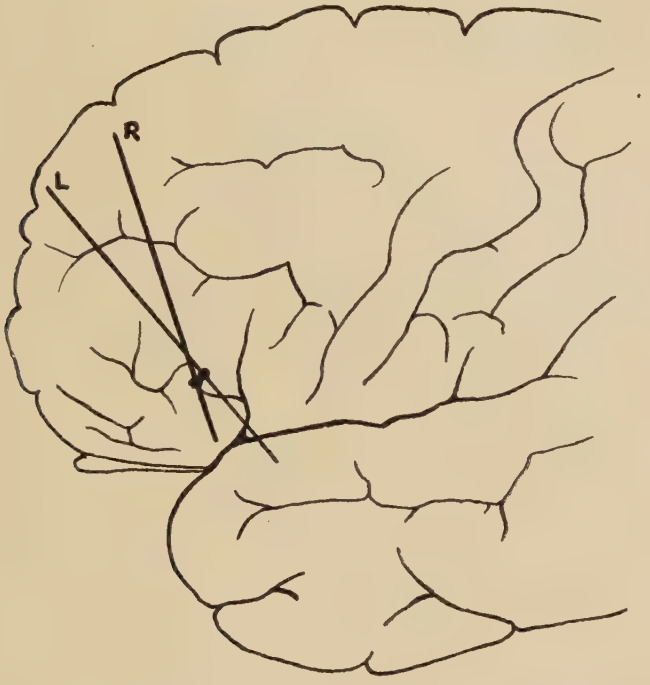

FIG. 1 (Case No. 59).—Showing the plane of the leucotomy cut in left and right hemispheres.

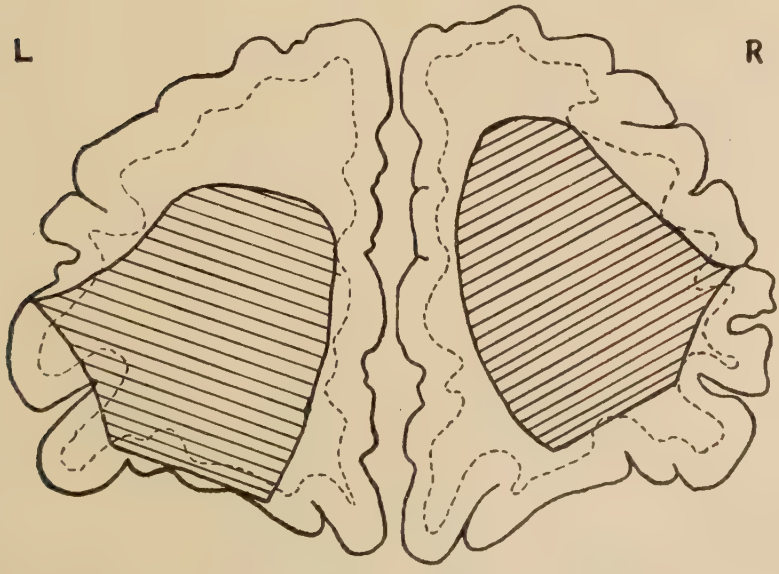

FIG. 2. (Case No. 59).—Showing the extent of involvement of the white matter and cortex in the two frontal lobes.

thank the Superintendent and the Clinical Director of the Crichton Royal, Dumfries, for permission to mention the more fully described case of post-operative respiratory failure.

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A PSYCHIATRIC REVIEW OF FIFTY CASES OF GUNSHOT WOUNDS SELF-INFLICTED.

By R. F. Fidler, M.B., B.S., D.P.H.

My interest in this subject was aroused during the first few weeks of the campaign in Normandy, when seemingly large numbers of these cases were known to be undergoing surgical treatment. At that time the rapid flow of psychiatric cases prevented a clear view of the significance of the situation as it was impossible to know accurately whether these wounded were in high proportion to the number of troops in action or to the total of battle casualties.

I recall that only once was I asked to see any patient with clinical anxiety among the first hundred self-inflicted wounds under treatment in a neighbouring hospital for whose psychiatric work I was responsible; this one case I saw had an exaggeration of the very natural fear of being shot after the expected result of his court martial; he was fairly easily persuaded to face his responsibilities and did not behave like a marked psychopath.

Three months after D-day I took an opportunity of examining 50 cases at a holding unit in the hope of distinguishing accidental from deliberate injuries in battle-strained men by psychiatric criteria as compared with the results of more purely military consideration. The cases were unselected and had been charged with "neglect in the use of weapons," and all convictions were in those terms; the usual decision had been taken as to whether the wounding was consistent with a missile from the man's own weapon; 29 had been sentenced and 21 awaited trial.

The cases were first seen by their Medical Officer during his regular examinations for a graded physical training course; they were then reviewed psychiatrically and a report sent to a medical board for any recategorization to take effect after completion of any sentence. My records included details of childhood and adolescent health, a social history and estimate of any pre-service neurosis, response to service training and stress together with an account of the injury without access to previous records; there was no question of extracting confessions from these men.

I. Accidental.

The interpretation of the stories and psychiatric histories of 22 of these men was, in my opinion, that of accidental injury. Two foot injuries arose from handling Sten guns; two occurred during demonstrations to mates of captured revolvers and the remainder during cleaning of rifles with resultant injuries mostly to one or other foot and less commonly the left hand or forearm.

There were 10 "reasonably stable persons" whose ages varied more widely than did those in any other group; they were from 19–38. The accounts of four of these accidents are found in the appendix; the first two, A— and

B—, had had more than two years' good service and had been through average battle stress without neurosis. The other two cases quoted, C— and D—, were both under 20 years of age and handicapped by psychological immaturity as well, and this was typical of the remaining group of 12 in this accidental series ; only one of whom was over 21. I have no doubt they were in a mild anxiety state at the time of their injuries after experiencing rather more than average battle stress, but the earlier histories of a few cases showed a type of mild constitutional psychopathy making them "accident prone." No more precise diagnosis than psychopathic personality (with emotional abnormality) was possible. The "reasonably stable" were left in Medical Category A on psychiatric grounds ; roughly half the unstable were placed in Category B and half in C.

It will be seen from a perusal of these examples that some of these accidents are preventable by routine inquiry into the psychiatric history of the men, if undertaken during their first few days in the General Service Corps ; intelligence and manual dexterity and other testing identifies gross cases of "accident-prone" persons. Suitable postings can prove prophylactic in the same way as driving accidents are to some extent prevented by postings away from such duties after tests. There are, however, bound to be cases that elude this net and in whom mild personality defects become more obvious during the cumulative fatigue and anxieties of battle and in whom, therefore, accidents occur. Personnel of the B.L.A. were fully tested before D day, but large scale changes in employment were impracticable. Improvements in the Sten gun were made soon after D day in view of these accidents.

II. Deliberate.

The five confessedly deliberate cases are quoted here in full :

Private E— sustained a fracture of the proximal phalanx of the left great toe, 19.vii.44, 1½ years after conscription at the age of 18½. He had become a Rifleman after satisfactory weapon training and settled down well with pre-service friends in a good and well-known Infantry unit mostly drawn from the same city as himself. He landed in Normandy on D plus 4 and had very little rest for five weeks, but he "got on alright," though several pals were lost. He stated that he "would not move from his trench during the last four days before he shot himself." He added that he saw others do this, but hesitated, and then having shot his foot he "felt foolish and did not like leaving his trench mates afterwards."

At the time of my seeing him two months later he had progressed well surgically and he was satisfactorily employed in the cookhouse, but he himself considered this too inactive despite incapacity from a foot-plaster ; he genuinely wished to return to full duty. He had informed his parents he had had an accident.

The earlier history was of healthy stock, one brother doing well in the Army and another a medical instrument maker, but another brother died nine months old with "fits"! After reaching the top standard of an elementary school he fulfilled his desire to become a butcher by apprenticeship, and liked the active life, attended sales, etc., with a cousin by whom he was employed. He had plenty of general interests and had a girl friend.

One's impression was of a good personality not suffering from any excess of remorse at the time of my seeing him ; he was making the best of things and realized that in camp the conditions were relatively easy. He received a sentence of two years' hard labour and this, in my view, would not lead in his case to deterioration in personality and diminution of his capacity as a soldier ; I recommended a change in category on psychiatric grounds.

Private F— fractured the neck of his third metatarsal, 9.vii.44, $1\frac{1}{2}$ years after conscription at the age of 18. He described how he " got on alright " and made friends in an Infantry unit for nine months and was then transferred to his present unit, where he did not find he fitted quite so well. He took part in the second assault on D-day, $\frac{3}{4}$ hours after H-hour, but this was " moderately uneventful " even though he lost most of his pals that day ; his unit moved forward continually until, on a general order to clean rifles, he was sitting outside his slit trench with the weapon across his knees ; he describes his pulling the trigger quite clearly. His attitude at the time I saw him was mildly insolent and he had no regrets.

The earlier history was of his father's dying when he was 10 with the almost inevitable dependence on his mother, whom he had informed of this injury in truthful terms, and in reply he was told he " was stupid " ; there were three brothers—one in the R.A.F., but the other two of unknown activity; he had " never taken any interest in them " ; he himself lived with friends in the same county as his mother ; he had had a girl friend, but they quarrelled and parted. He reached one standard from the top of an ordinary elementary school and became a carpenter's apprentice for three years but gave it up and became a lorry driver.

The general impression was of a poor, immature personality of schizoid type, though of average intelligence. His attitude to his 12 months' detention was not remorseful, he was sullen and disliked being employed in any form ; his injury was improving at an average rate. Medical Category C was recommended.

Private G— produced a comminuted fracture of the proximal phalanx of his right foot, 4.vii.44, by a shot from his rifle. He had volunteered at the age of 18, 8.xii.42, " because everybody else seemed to be in the Army " ; he was placed in the infantry but would have preferred R.A. as " you seem to get better treated there."

He took part in the 2nd assault on D day at 9.30 a.m. and his unit was active for four weeks with two 4-day rests ; he disliked mortaring more than going into an attack, but on this last action he described how he had the safety catch of his rifle forward and how he " then felt nervous, found his foot stung and that he had a hole in his boot." He mentioned that he felt off his food for 48 hours before this and that " more than likely he pulled the trigger."

The earlier history was of leaving the top form of an elementary school at the age of 14, but went to a doctor for his " nerves "—he was " full of funny ideas that he lost in the Army." The parents sound stable, but were concerned about their son's situation to a natural extent ; there was one healthy sister, no girl friend, but several pals some of whom he had heard were killed in Normandy ; his job was that of a lathe operator and he was a boxer.

The general impression was that of a youth somewhat duller than his educational attainment might suggest and more immature even than his age would warrant ; he thought he would be greeted with enthusiasm on return home after completion of sentence. The case had been adjourned owing to failure of witnesses. In view of his psychiatric handicap I did not consider that punishment would improve his capacity as a soldier and recommended Category B.

Private H— fractured the 1st, 2nd and 3rd cuneiform bones of his left foot by a rifle shot, 9.viii.44. He had volunteered for the Army at the age of 18 and had served 4 years as a cook the whole time. He declared he had had no infantry training and had not handled weapons because the battalion had just returned from abroad at the end of May, 1944, and " all courses had been stopped." After no embarkation leave he had served three weeks in the line out of two months in Normandy and felt " nervy all the time." He said he had been on guard and " it wasn't an accident really."

The earlier history was that his father died when he was 5 and as his mother committed suicide when he was 14 he went to live with an aunt. He attended an elementary school, but was sent to a convalescent home at the age of 11 " for nerves," but he returned to finish at his ordinary school at the age of 14 ; he left from the bottom form, but he was under the impression he " had made up for it since "—he could only just read and was still excessively afraid of the dark. He had been employed by several different firms as a polisher and in each had had accidents, none of which was seriously disabling, but he was dismissed from each because of this. There were two brothers; one was burnt in an Army tank, but recovered after treatment ; the other was doing well in the Police force.

This man gave the impression of being a dull, inadequate personality with a

bad background, but he was coping with his environment as well as he could; I did not think that punishment would make him a better soldier; I recommended Category C, but his case had not yet come before the Court.

Rifleman I—, after 10 months' service from the age of 18, had wounded his left foot, 12.vii.44, with a rifle shot. He had been 3½ weeks in the line and had had a gradual onset of nervousness and felt "shut in" whilst in a trench; he had been experiencing battle dreams and was upset at seeing and attending to casualties; he had had no mail from home since being in Normandy and he had wandered away once but gave himself up; he was rather vaguer than most of the 50 cases as to details of his movements in France. During cleaning his rifle he described how he had an uncontrollable impulse to injure himself.

The earlier history was of conscription during November, 1943, but he did not recall the date without verification from A.B. 64 as the 18th; he disliked the six weeks' preliminary training because it "made you feel you haven't a mind of your own"; then after ten weeks' infantry training he attended a signals course with poor result and after that a "hardening course." He proceeded to Normandy "sometime in July" and thinks he was four weeks in the line as a runner; he saw his two pals mutilated, and his description of response to the call for first aid was that of more than average fear.

The background was of the father a Chief Clerk to the D.C.R.E.; a happy home of three brothers, the eldest to Consular service after Cantab.; the second, a mortarman instructor who had never been in action, "thank goodness," according to my examinee, the youngest of the four; the third brother had been in the Army, but discharged for some condition not identifiable from this man's description. He left an elementary school from the top form and was happy there; he became a clerk but made five changes in four years without any definite reason and had suffered from a compulsive desire to throw himself off bridges. At the time of my examining him he was irrationally fearful of returning to his unit; he considered the condition of his foot would not prevent his being sent and had no idea that S.I.W. had solved his problems even temporarily; he found he had not the courage to inform his family other than in terms of accidental injury.

The impression he gave me was of a poor personality of schizoid type on whom I considered the effect of punishment would be negative. He confessed to a deliberate action during his 90 days' field punishment given for "negligence in handling a rifle." I recommended Medical Category C.

It is notable from this group that none had been evacuated earlier in the campaign for battle exhaustion; from their stories it is likely that they were so suffering at the time of their incidents. One was surprised at the variation in the degree of psychopathy that seemed necessary to produce these acts. The first case was an average personality but the others showed deviations. This small clear-cut group were all young and psychologically immature and not readily diagnosable by set labels indicating particular types of neurosis; none was near any dangerous state of depression at the time of his incident; the nearest label for administrative convenience was "psychopathic personality with emotional abnormality."

These service findings are striking contrast to civilian experience of the gross degree of constitutional psychopathy in hysteric form that one usually associates with such lesions as dermatitis artefacta. On the general principle that battle neuroses are the result of the interplay of constitutional and environmental factors in childhood with later stress, any interpretation of these five deliberate S.I.W. cases is that the latter factor predominated rather more than it does in any unselected series of neuroses from the field. Had they been more handicapped by a greater degree of constitutional predisposition to neurosis their training stress would have eliminated some of them from the risk of

battle stress ; if they had been in any appreciable action they would have broken down earlier and appeared at Field Dressing Station level of evacuation.

They were, to a considerable extent, comparable in type of psychopathy to any series of immature deserters from equivalent battle stress but, on the other hand, they had coped with their innate handicap better and displayed greater stamina in that they faced the possibility of an immediately painful result of their acts more consciously than does the hysteric wanderer who is often near a fugue state at the time of desertion. The prognosis, however, was not as good as their comparatively slight psychiatric handicap suggested ; their chance of return to full duty was slight quite apart from any residual disablement from their injuries. The delay from surgical and legal necessities tended to prolong any neurosis, especially as really useful occupations had been difficult to organize ; the outlook was nearly as bad as that of some soldiers not markedly psychopathic but lightly wounded by enemy action, who had spent three to four months in general hospitals in Great Britian but who broke down within three weeks of return to action.

Even though some of the statistical evidence may never become available, I think it is fair to compare these cases with the impressions gained from the various administrative levels at which battle neuroses were dealt with in the B.L.A. ; when their proportion rose during the mounting total of surgical casualties the number of neuroses never became really serious and at the same time neither did the self-inflicted wounds become a serious problem. It would be somewhat difficult to prove satistically whether these cases were more common in the B.L.A. than during 1914–18 or *vice versa* ; it is possible that some of our neuroses treated from June, 1944, onwards would have been self-inflicted wounds if they had served in the 1914–18 War, because then the death penalty for desertion was current and clearly enunciated.

III. Doubtfully Accidental.

There were 23 men whose military situation was more difficult to define from assessment of their stories even in the light of their psychiatric histories, hence their interest was as much medico-legal as clinical. Descriptions of four of these cases (J— to M—) are found in the appendix.

The general impression one received from their stories and their attitude to detention and their future was, on the whole, consistent with their backgrounds. Many were resentful at being punished for acts they considered not their own fault, and this seemed to be genuine rather than a cover for guilt in many cases ; only a few of the more psychopathic " protested too much " ; most were thankful at not being available for full duty again, but this did not seem to me outside normality. A few of the more doubtful stories indicated the possibility of deliberate acts, especially in view of the psychiatric histories ; the lack of ability to confess was consistent with the degree of psychopathy ; there were a few, however, whose lack of confession was probably in order to prevent an increase in anxiety that had arisen from the difficult domestic situations. These latter cases were older men who from that factor alone would be more likely to be thus handicapped quite apart from any inherent

psychopathy ; 7 of these 23 men were over 30, with an average of two years' service. In a few instances quite markedly handicapped men had survived surprisingly more than average battle stress before finding themselves in a position of temptation to self-mutilation, yet such could not be proven to have occurred from legal or medical evidence : cases J— and K— illustrate some of these points.

The age range was 19–34, five of them being under 21, with mild psychopathy similar to that of the five deliberate cases, but the incidents occurred whilst the men were cleaning rifles at rest, as did all but two of this group ; these two were chronic mild hysterics, aged 29 and 32, one of whom had 7 years' service, mostly as mess orderly ; then incidents occurred during action whilst they were in a condition approximating to a fugue. No other hysteric manifestations were found such as palsies complicating wounds. I was able to place only two in a medical category higher than C, and they were the only ones in which I could say that punishment might be beneficial.

There were 8 dull and backward men, whose instability was of a type commonly associated therewith ; their incidents occurred under field conditions less exacting than any other group, they were both more liable to accidents and to deliberate injury because of double handicap. The first case shows how repeated postings was a stress to which this type is particularly liable and vulnerable ; the second man was, on the other hand, among friends all the time but was more handicapped by innate defect. All these 8 were more depressed than others in the camp ; in none did I recommend a higher category than C. It is of interest that they were in higher proportion to the normal 10 per cent. or so usually found amongst any unselected recruits during routine examination in the General Service Corps.

The difficulties of standardization of individual responsibility above the level of the obvious psychotic are only too well-known in civilian practice. The use of psychiatric reports on military crimes has been found to confirm civilian figures ; about 2 per 1,000 examined can be deemed irresponsible from psychosis ; no psychotic cases appeared in this series owing to immediate segregation in special hospitals.

These 50 cases are summarized by tabulation as below :

	Sentenced.	Not sentenced.	Total.
I. *Accidental :*			
(1) Occurring in reasonably stable persons	5	5	10
(2) Occurring in unstable personalities	8	4	12
II. *Deliberate*	3	2	5
III. *Doubtfully accidental :*			
(1) Occurring in unstable personalities	9	6	15
(2) Occurring in dullards with associated instability	4	4	8
	29	21	50

I placed 12 unstable personalities in Group I (2), owing to a considerable degree of inherent psychopathy, and took extra care over their stories of wound-

ing, because one would naturally expect to find greater difficulty in interpreting their military situation. Absence of witnesses was the cause of delay in sentence of the five "reasonably stable persons" in Group I (1) and to a very great extent this was inevitable at that stage of the campaign; the fact that so many fall into this group might suggest a greater degree of responsibility than "accidental injury," but the evidence as a whole does not, I think, support such a contention. It seems to me fair to say that even if the 23 "doubtfully accidental" wounds could have been proved deliberate this would still leave 22 "Accidental" that would then stand out perhaps in somewhat false contrast; at any rate, whatever figures might result from differing examiners with extra or predominantly legal or medical outlook, there is, to my mind, a not negligible proportion of accidents with weapons among these soldiers.

Summary.

1. Most cases of self-inflicted wounds whether deliberate or accidental in men from battle areas are early cases of exhaustion neurosis.

2. S.I.W.'s are uncommon relative to total casualites and also to other types of neurosis under field conditions.

3. Few of them can easily be proven to be deliberate, and those that are so are drawn from similar psychiatric material compared with the variations one meets in unselected cases of battle neuroses; they were immature youngsters, genuinely exhausted.

Review of Literature.

American writers tend to equate S.I.W. with malingering. Bishop (1) defines the self-inflicted injury as "hurt of any part of the body whereby he is rendered less able in fighting either to defend himself or annoy his adversary." Clark, in the same publication, adds that criminal acts of this type do not include those that disfigure, such as cutting off the nose.

The incidence amongst conscripts in the U.S.A. was considered high enough for special instructions to be issued to Recruiting Boards reminding them to keep a watch for these cases (2). Bruinewitsch (3), early in 1939, found a wide variety of ruses to avoid military duty and considered them to be common; he described various chemical burns and even very unintelligent damage to the skin to represent through and through chest wounds; none of these can be classed as occurring after military stress.

Civilian experience is quoted from 14 cases of dermatitis artefacta by D. Hart and R. Jones (4): these occurred among young women of subnormal intellect and cases in men were more clearly related to sexual perversions of masochistic tendencies.

The only writer describing any case in a military setting was D. J. Flicker (5). He was attempting to provide a court martial with a report on a soldier on Home Service who, after moderate prompting, was able to recall details of placing his hand under a passing railway train in order to get leave to go home; this had neither been requested nor refused; examination showed him to be of intelligence corresponding to a mental age of 13 and showed

general psychological immaturity of hysteric form. The psychiatrist did not feel confident in recommending prosecution for malingering; the report was rendered to term of "no psychosis." In this paper he quotes Emanuel Miller as implying that S.I.W.'s were common in the 1914–18 War by wording "entire hospital wards were filled with men who had been shot in one finger or one toe. No one will ever know fully how many of these were self-inflicted injuries, although medical officers then on duty believe the number to run into thousands."

Perusal of Emanuel Miller's book itself (6) shows a review of the literature of war psychiatry to 1940; there are exceptionally few references to the subject of S.I.W.'s and the author quotes none. He mentions his own clinical experience of a tented field hospital where the instability of S.I.W. cases was as great as that of "shell shock" cases (as battle neuroses were then called); he considered the former to be in the prodromal phases of neurosis, the patient being in a state of pathological dissociation when the attempt was made.

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Appendix.

I. (1) Accidental wounds occurring in reasonably stable persons.

Sergeant A—, aged 29, with 4½ years' good service as infantryman, was sent overseas with the B.L.A., D plus 8, and reached a forward area 14 days later. He had three spells there totalling three weeks and declares that he "got on alright" and was promoted to sergeant; this was not wholly explained by the fact that two battalions had to be merged owing to casualties during a break-through at the end of August. He, like many of his mates, acquired a German revolver about which he fancied he knew something. He was demonstrating this by pulling it apart; it went off and wounded his left hand, leaving him with a fractured neck of the second metatarsal; he was right handed. The earlier history was good psychiatrically; he had an average result at an elementary school followed by progressive employment. He came from a healthy family with a brother on service in Burma and a sister in the Q.A.I.M.N.S. Marriage was successful, with two children. His morale was good and his attitude to his military situation sensible.

Private B—, aged 27, with 4½ years' good service all in the same infantry unit, had enjoyed his six weeks' period of training. He had been in Normandy since D plus 16, at Caen and Falaise, but had "got browned off owing to mortaring and night work." He described a "routine job" of cleaning his rifle at 6 p.m. after having been on guard at night, unable to sleep in the day-time and had been up since 4 p.m.; he was talking to his mate 5 ft. away when "there must have been a round in the breach, unknown." He declared credibly that he had "always been very careful." He was of a large healthy family—this member had an unlucky marriage, but he had the stamina to cope with it well and could not be said to have

neurosis associated therewith ; his work had been that of gardener after average elementary school curriculum. I considered he was in a very mild anxiety state at the time of the incident but this had passed. His morale at the time of examination was good.

I. (2) Accidental wounds occurring in unstable personalities.

Rifleman C—, aged 21, with 4 years' service, had volunteered 11.xi.40, because of unemployment. He was under the impression that he had acquired weapon training satisfactorily. He took part in the second assault on D day and later was stationed just outside Caen for a month. He was given a Sten gun on being promoted to No. 1 on the mortars. He declared that he had never used this weapon before and was cleaning it across his knees when it exploded and wounded his left forearm extensively. His origin was from exceptionally poverty-stricken location with an unhappy family background ; employment had always been irregular and of low grade ; he was below average in intelligence and unstable in addition, yet he was not unduly strained by battle ; the story was consistent with a highly accident-prone person.

Private D— smashed his proximal interphalangeal joint of the 2nd left toe from a rifle wound, after 1½ years' conscripted service from the age of 18½. He had been in several infantry units but managed to make friends ; he had been trained in a beach group and landed in Normandy with the first assault troops on D day and remained on the beaches for two months, unloading craft. Then, after a few days in two attacks in the line, he felt nervous " after plenty of shell fire " and then lost his pal and " didn't know if his nerves went." He did not see his M.O. and continued in action for a week ; one day he was outside his trench cleaning his rifle when he was obliged to get back owing to mortaring but got out again to finish the cleaning, " it went off during the final rub over." He did not know how it happened, " he did not remember pulling the trigger."

The earlier history was of the death of his mother when he was three, with the not uncommon failure of the substitute and early marriage "to get away from home." This had been satisfactory judging from the man's letters home, but he felt unable to contradict the local paper's account of his having been " wounded in action." There had been an average result at an elementary school and fair work record ; the impression was that of a person mildly handicapped by constitutional psychiatric defect ; his morale was fair considering this ; he expected to break down if he ever became fit surgically for Category A duties but looked forward to doing his best should he be made a driver ; he showed some skill at maintenance work. I did not think that punishment would necessarily improve his capacity as a soldeir. I recommended Category B.

III. (1) Doubtfully accidental wounds occurring in unstable personalities of average intelligence.

Private J—, aged 34, with 1 year 9 months' service, was conscripted 19.xi.42, after volunteering in 1941, but was not accepted because he was a foreman joiner in an Ordnance factory. He received 14 weeks' infantry training but was then placed in the cookhouse because of loss of the left forefinger in civil life ; this had proved a difficulty with the rifle. In Normandy from D plus 7 he was a cook in a holding unit for a month and then a reinforcement to a well-known infantry unit, but he did not experience strain over more than a few days and he was due out of the line the next day, he stated. His story of the wounding of his left foot was that there was difficulty in getting the pull-through out of its container in the butt ; the opening had become stuck. He used a tin-opener with the rifle upside down on his foot—the " usual position to do this " and " something caught " ; he added " somebody must have borrowed it and left it loaded." He sustained a compound fracture of the proximal phalanx of the 2nd toe. The civilian history is that he has been married 12 years and had requested welfare investigation of his wife's alleged infidelity at the time of the incident ; he was taking his troubled circumstances well. He described himself as always having been a nervous type excessively afraid of the dark and of strangers ; he found he was happier making drawings in his spare time even though he was engaged on joiner's work all day. He was an inadequate personality that could have been equally capable of a clumsy accident as of more than " negligence in the use of weapons." I recommended Category C, on psychiatric grounds.

Private K—, aged 31, with three year's service, wounded his left foot with a shot from his rifle, causing a fracture of the 2nd and 3rd metatarsals. He had

been conscripted 26.vii.40, and placed in a well-known infantry unit but did little beyond driving duties. At this time his wife was twice " bombed out " with the result that he deserted for a year and was duly punished. He went to Normandy 1.vii.44, and after being in reserve for a fortnight spent a week in a forward area, when he stated that having cleaned his rifle he was sitting down with the barrel facing downwards, chatting to a mate—" It just went off ; did not know whether it was hand or rifle." He explained that he was feeling disgruntled at the time about not having had embarkation leave. The earlier history was somewhat erratic ; he was backward at school which he explained as due to " general circumstances of his home." The background sounded very unhelpful, but this is not wholly the explanation of his neurotic tendencies. He failed to complete an apprenticeship at electrical engineering after 18 months and drifted into casual labourer's work in building. It seems to me that had this man not had this questionable accident he would have turned up with some other form of psychopathy, absence without leave or a hospital neurosis case. I recommended Category C.

III. (2) Doubtfully accidental wounds occurring in dullards with associated instability.

Private L—, aged 22, with 11 months' service, had been conscripted 4.xi.43, and had like his infantry training and appears to have done reasonably well on weapon training and with the B.L.A. from D plus 10. He appears to have had an easy time for the first few days but was transferred to another unit that ran into a difficult patch under mortar fire—there were some desertions from the unit. He then had two days' rest and was transferred to yet another unit and had been in action all day, had had no sleep the night before the accident, and whilst cleaning a rifle he described how he " pulled the trigger, having the rifle brush in the same hand with the weapon across his leg " ; he added " there must have been a bullet up the breech." He sustaind a wound of the left foot with a compound fracture of the head of the 1st metatarsal. He was depressed at the time of this description —three months after the injury—and it is likely that he was of as poor morale then as at the time of the injury. The earlier history is that despite regular attendance at an elementary school he left at 14 half way up the school and illiterate. He followed a family tradition of entering a coal mine, but was found to be unfit for underground work owing to tachycardia, so he left in August, 1943, to work in an aluminium factory and got on alright there. There were two brothers of better intelligence, one on a farm and the other in a factory. He had always been exceptionally shy and one's impression was that this was an immature dull youth of the type more likely to be tempted to semi-conscious evasion of the strain of forward areas ; he was also accident prone from his low intelligence so that an opinion on the possibility of deliberate injury could be no more certain than that already provided by the Army legal arrangements. Category C was recommended.

Private M—, aged 20, with 18 months' service, injured his left foot with a rifle shot, causing a compound fracture of the medial and external cuneiform bones. He had volunteered for the Army 3.xii.42 " because his mates had joined," he was vague as to how he had got on during infantry training, but he had settled in the regiment to which he was posted because he had met mates from his home town. He took part in the second assault on D day and then was part of a beach group unloading under fire for a month ; later he moved about a good deal without being in action. He was cleaning his rifle " because it was raining, but had been told to keep it loaded for a break-through." He gave a slow description of taking the magazine out and of putting the rifle on the bank at the side of the trench in order to facilitate extraction of the " pull-through," he picked up the rifle again and placed it muzzle downwards on his left foot. In cleaning with a rag the trigger became caught and the shot was fired. (One had heard a similar story from all kinds of men of different units, but one received the impression that this youth was too dull to have been coached in his story.) The earlier history is of reaching two standards from the top in an elementary school and then working in his father's florist's shop ; he was only interested in solitary pursuits and he had broken off with a girl friend. Category C was recommended.

THE RESULTS OF TREATMENT OF A THOUSAND CASES OF SCHIZOPHRENIA.

By L. A. Finiefs, M.D.Paris, D.P.M.,
Deputy Medical Superintendent, Three Counties Hospital, Bedfordshire.

The cases reviewed in this paper were treated in Three Counties Hospital during the last seventeen years. The ages of the patients ranged between 15 and 44 years. Of the total 1,009 cases, 563 had insulin coma and convulsion therapies, while 446 received no such special treatment. Some had prefrontal leucotomy after failing to respond to insulin and convulsion treatments, but their number is small and they are not included here.

All cases had the same general management and nursing care. Those who were or became accessible had superficial or minor psychotherapy consisting of simple explanation and discussion of their problems and the nature and origin of their illness. In addition they had some form of occupation therapy.

In Table I is shown the total number of cases, their rate of discharge and their average stay in hospital, also the period with which their stay in hospital coincides. The response to the treatments of the clinical types of schizophrenia and an attempt at the prognosis are not dealt with here. They will be the subject of another communication.

Diagnosis.

All the cases were well known to me and the diagnostic criteria are therefore essentially the same for every group included in this survey. Aubrey Lewis (1935) stated that, "Schizophrenia may be regarded for diagnosis and other clinical purposes as a form of maladaptation in which there are certain characteristic defects of inner harmony and consistency in behaviour, thought and emotion." The term schizophrenia being applied not to a definite disease, but to a clinical syndrome, the cause, pathology and course of which are uncertain, the views held as to its causation have largely determined the criteria of the diagnosis.

According to one theory schizophrenia is essentially of organic origin, the presence of which in a patient is signified by certain "process" symptoms occurring in those prone to the disease through constitutional factors. Psychoses of this type are the true schizophrenias. Schizophrenic symptoms may also occur in cases which are not thought to be liable by virtue of constitution to true schizophrenia. These latter cases are the atypical schizophrenias or "schizophreniform" psychoses. Langfeldt (1937) states that true schizophrenics show bad prognosis, while mixed and atypical cases in whom there is a strong admixture of manic-depressive and symptomatic trends exhibit a more favourable course.

Another view of its causation on which diagnosis can be based is that of "reaction formation" of Adolf Meyer, who does not consider schizophrenia as of purely organic origin (Henderson and Gillespie, 1944). While recognizing that the individual may be loaded in various ways by inheritance, by physical defects of an endocrine disorder or some grosser kind, none of these is in itself a sufficient cause for schizophrenia. It is only when the subject has to battle with life's problems that reactions appear which cumulatively lead to a schizophrenic condition, and he concludes that schizophrenia is the end-result of faulty habits of reaction.

The diagnosis of the cases in our series was made after observation for a reasonable time and after taking into consideration the heredity, life history and prepsychotic personality, the history of the illness and previous attacks. In this survey are included only those cases in which the diagnosis of schizophrenia could be made with confidence on clinical grounds. Doubtful cases, those who matured into atypical manic-depressives, the feeble-minded and psychoneurotics with episodic schizophrenia which cleared up very rapidly, were excluded.

The duration of the psychosis was very difficult to assess accurately, and it was impossible to determine when the onset was insidious. Therefore, the time stated in Table II is approximate and implies the period from the first noticeable change in the personality of the patient up to his admission to hospital. As is generally recognized, and our remission rate confirms it, the prognosis is most favourable during the first year of overt illness, whether expectant or physical treatment is employed. It becomes gradually less promising.

Classification of Results.

For recording the results classifications were suggested by Muller (1936), James, Freudenberg and Cannon (1937), Hunt, Fieldman and Fiero (1938), Guttmann, Mayer-Gross and Slater (1939). I agree with Blair (1940) that over-classification with divisions and sub-divisions is confusing, and have classified the results into (1) Much improved (synonymous to recovery) : Those sufficiently recovered to carry on at their old employment or other work equivalent to it. This implies disappearance of all active psychotic symptoms and the return to a substantially normal life in the community. (2) Improved : Those who improved sufficiently to be discharged from hospital to sheltered surroundings and able to carry on with less responsible work than previously, having not regained insight into their condition and retaining some residual symptoms. (3) Unimproved : Those who have to remain permanently in a mental hospital and the few who are removed by their relatives to be looked after as invalids at home, unemployable and vegetating.

For brevity, only the much improved and improved are given in Table I.

Cases which Received No Special Treatment.

This group of 446 cases received no special treatment beyond ordinary nursing care, routine hospital life, attention to physical health, some occupation

therapy and the psychotherapy of friendly interest. Their improvement may be considered as being the nearest to spontaneous remission.

The majority of them were admitted to hospital before 1937, when insulin and convulsion therapies were commenced. After that date and up to 1942 there were still a number whose relatives objected to their being treated by these methods. Since 1942 all cases admitted have received some form of special or physical treatment. Of the 446 patients in this group, 156 (34·5 per cent.) were discharged. Their average stay in hospital was 8·3 months.

Cases Treated with Convulsion Therapy.

Treatment with convulsions as first suggested by Meduna (1935) was carried out by injection of camphor derivatives, cardiazol (metrazol) intravenously and triazol (azoman) intramuscularly. This method was superseded by that of Cerletti and Bini (1938), who induced fits by the passage of electric current through the head. A fit was induced every other morning and an average of 17 were given. At the beginning we had a few complications, such as dislocation of the jaw, and in one instance of the shoulder, and a few crush injuries to the bodies of the middle thoracic vertebrae, from which no deformity or disability followed. No fatality occurred. Later, as the technique improved, we had no complications.

Convulsion therapy was introduced into this hospital in 1937, and 82 schizophrenics were treated, 32 (39 per cent.) of whom were discharged. As a treatment for schizophrenia, however, it was realized that convulsion treatment alone did not give the results which its originators claimed. The improvement obtained was frequently not very stable. Fits (an average of five) were combined with insulin coma therapy and were found to be useful in sensitizing the insulin-resistant and to stimulate those whose improvement with insulin remained stationary over several comas. One hundred and three cases were treated with this combined method, and 56 (54·3 per cent.) were discharged.

Cases Treated with Insulin Coma Therapy.

Sakel's (1935) technique, which was used here, consists in injecting daily increasing doses of insulin until a coma dose is reached for each patient. Hypoglycaemic comas were induced five days a week, the duration of the coma being gradually increased from 20 minutes to an hour, when the patient was given glucose through a stomach tube or intravenously in order to regain consciousness. On awakening the patients were more accessible and some psychotherapy was used in the form of suggestion and reassurance. A course of treatment consists of 30 to 50 comas.

This treatment was started in this hospital in 1937, and was continued during the war in "The Homestead," a convenient villa in which 18 patients of each sex could be treated simultaneously. It was fortunate that the same trained staff was available throughout that time.

Of the 378 cases treated, 206 (54·2 per cent.) were discharged. The average number of comas was 34. It is known, and my experience confirms this, that

comas are essential in bringing about improvement. Modified insulin therapy, for which only sub-coma doses are used, is not satisfactory as a treatment of schizophrenia. No fatality occurred in our series. At the beginning we had some complications; one patient had severe laryngeal spasm and another oedema of the lungs. Fits in hypoglycaemia were fairly frequent, but the commonest complication was delayed return to consciousness. With experience and improved technique, however, the occurrence of complications was reduced considerably.

Follow-Up.

Discharged patients were instructed to attend at intervals our Psychiatric Clinics for interviews. A simple questionnaire is also sent to the nearest relatives, requesting them to give their views on the patient's mental condition since discharge (and if possible to supply a comparison of his present condition with that previous to his illness), to give information about relapses and also the periods of employment and unemployment and the form of work he is doing. Our social workers supplement the information by their visits.

The follow-up of the group of 156 patients discharged after receiving no special treatment revealed that—

10 were out of hospital and well for 12 years and over.
12 ,, ,, ,, 10 ,, ,,
16 ,, ,, ,, 8 ,, ,,
25 ,, ,, ,, 5 ,, ,,
9 died.
62 relapsed.
22 were not traced.

Thus, 63 patients, 40 per cent. of the 156 discharged, or 14·1 per cent. of the total 446 reviewed, are known to have kept well for five years and over, while 62, 39·7 per cent. are known to have relapsed.

In order to compare the above findings with those of the group which received special treatments, only the results of the follow-up of patients discharged five years and longer will be given. From 1937 to 1942, 312 cases were treated with insulin and convulsion therapies, 188 were discharged as greatly improved and improved. Their follow-up shows that—

25 were out of hospital and well for 10 years
39 ,, ,, ,, 8 ,, and over.
53 ,, ,, ,, 5 ,, ,,
4 died.
54 relapsed.
13 were not traced.

Therefore, 117 cases, or 62·2 per cent. of the 188 discharged patients, or 37·5 per cent. of the total of 312 cases of this group, are traced and are known to have been well for five years and longer, while 54, or 30 per cent., relapsed.

Conclusions.

Comparison of the results obtained show that there is no specific treatment of schizophrenia. It may be stated, however, that apart from more rapid and more frequent improvement, the quality of the improvement was a striking feature of cases treated by insulin therapy. The patients who responded to it soon became brighter, with genuine spontaneity of conversation, interested in themselves, their illness and their surroundings, and gradually began to plan for their future. Their improvement is also more durable. The follow-up reports of many of these patients contain such phrases as, " Doing well, working regularly since discharge, excellent health, no relapse, leading normal social life," etc.

The average stay in hospital of the non-treated cases was 8·3 months, as against 5 months of the treated. The shortening of the sojourn, apart from the economic gain, has a favourable effect upon the whole attitude of the patient towards himself and his illness. It is noticeable that the presence of improving patients in a ward soon creates an atmosphere of optimism which is the basis of successful psychological approach.

Insulin and convulsion treatments are considered to be empirical, as no satisfactory rationale has so far been found. Insulin therapy produces in most patients a great improvement of the physical condition, and factors such as treatment within a friendly group (separated from the bulk of other patients) and receiving daily active treatment and attention, undoubtedly contribute towards their mental improvement. Patients soon realize that a serious attempt is made to assist them in getting well and that they are not left to struggle out of their illness by more conservative measures.

Summary.

The results of the treatment in a county mental hospital of 1,009 cases of schizophrenia extending over 17 years, is recorded.

The recovery rate for all the patients is shown as related to the duration of their illness.

For the purpose of evaluating methods of treatment two groups were considered—one consisting of 446 cases who received no special treatment and

Table I.—*Total Number of Cases Treated and Discharged, and Average Stay in Hospital.*

Treatment.	Number of cases treated.	Greatly improved and discharged.	Improved and discharged.	Total.	Percentage.	Average stay in hospital from admission in months.	Period.
No special treatment	446	58	98	156	34·5	8·3	1930–1942
Convulsion therapy (cardiazol and E.C.T.)	82	11	21	32	39	4·8	1937–1944
Insulin coma therapy	378	96	110	206	54·2	5	1937–1947
Insulin coma therapy with few convulsions	103	24	32	56	54·3	5·2	1937–1947
	1,009						

TABLE II.—*Results According to Duration of the Psychosis.*

	Number of cases.	Discharged greatly improved and improved.	
		Number.	Percentage.
Symptoms 0–1 year.			
No special treatment	208	103	49·5
Convulsion therapy	38	20	52·6
Insulin coma therapy	176	130	73·8
Combined insulin coma with convulsions	42	32	76
Symptoms 1–3 years.			
No special treatment	137	43	32·1
Convulsion therapy	26	10	38·5
Insulin coma therapy	122	64	52·4
Combined insulin and convulsion	39	21	53·8
Symptoms 3 and more years.			
No special treatment	101	10	9·9
Convulsion therapy	18	2	11
Insulin coma	80	12	15
Insulin coma and convulsion	22	3	13·6

the other included 563 cases treated with insulin and/or convulsion therapies. The follow-up of the cases that were discharged for five years and longer showed that 14·1 per cent. of the first group were out of hospital and known to be well, as compared with 37·5 per cent. of those of the other group.

Mention is made of a few factors which contribute to the improvement of the patients treated with insulin therapy.

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OBSERVATIONS IN ELECTRICALLY-PRODUCED EPILEPTIC CONVULSIONS.

PART I.

Tonic Neck and Labyrinthine Reflexes upon the Eyes.

By R. Klein, M.D.Prague, and D. F. Early, L.R.C.P.&S.I., D.P.M.,
Bristol Mental Hospital.

The pattern of the epileptiform fit produced by electric shock treatment is fairly uniform and constant. The four stages of the fit—the preconvulsive, tonic, clonic and post-convulsive phases—are characteristically expressed in postures and movements of eyes and head in each phase.

In the preconvulsive stage, which is usually of very short duration, the posture of the head does not undergo any change ; there is no contraction of the neck muscles nor of any other muscles of the body, as can be ascertained in delayed fits when this stage is prolonged. In this stage the eyes are most frequently found in a downward position. In the tonic phase, in an uncomplicated fit, the neck muscles contract and carry the head into strong retroflexion ; usually, as soon as this occurs, sometimes after a short interval, the eyes turn straight upwards. This movement is more abrupt and rapid when the interval between the preconvulsive and tonic phases is short ; it is a relatively slow movement when the interval is prolonged. Commonly the eyes remain in straight upward deviation throughout this phase. During the clonic phase this position, together with the retroflexion of the head, is maintained in the majority of cases ; it is not unusual that the eyes are found in a lateral upward position towards the end of the clonic stage. In the post-convulsive stage a lateral upward or a purely lateral deviation is present. The eyes are seen to leave this position after an interval of half to one minute, either to move toward the midline or toward the contralateral side, and slow gliding movements from one side to another may subsequently follow. Later, when the patients become restless, the eye movements tend to become irregular and jerky, nystagmus-like movements being frequently seen.

The head and eye movements in the delayed fits will be described specially ; they are characterized by prolongation of the preconvulsive stage from a few seconds up to about a minute. The general tonic spasm starts with lateral deviation of the head, and usually after some delay the eyes follow the head with a slow, giding movement in the same direction until they reach the extreme lateral position. Both head and eyes remain in this position throughout the tonic phase, while in the clonic and following post-convulsive phases they usually take up the same positions as in the uncomplicated fits.

The eye reflexes which we observed will be described for each phase separately :

During the preconvulsive stage, if one turns the head to one side the eyes make a compensatory movement to the opposite side, and remain in this position as long as the position of the head is maintained.

In the tonic phase, in which the head is firmly fixed by the tonic spasm, the simplest passive movement to accomplish is the turning of the entire body. If the body be turned to one side, the eyes invariably follow the body, i.e. the eyes move in that direction in which the shoulder is lifted ; if the left shoulder be lifted to an angle of 90 degrees the eyes will go into the extreme right lateral position, and will remain there as long as this position of the shoulder is maintained. If the body is then allowed to return to the supine position the eyes will again take up their previous position—that is, an upward deviation in the midline. The same effect can be obtained when the head is passively turned to one side ; if the head be turned to the right, the chin towards the right shoulder, the eyes will go into the right lateral position. The degree of the reflex movements of the eyes is about the same in both these experiments. The response is distinct and of the same character when the head is rotated, or when one side of the body is lifted to right angles while the head is fixed in the midline ; under both these circumstances the eyes move in the direction of the passive turning, but the reaction is not maximal, as in the first two conditions. The head is retroflexed, the eyes in upward deviation, during the tonic phase ; if one turns the head passively downward, the eyes move down and keep this position as long as the head is ventroflexed ; as a rule the eyes do not go beyond the midline. Because of the convulsive spasm, and of the short duration of the fit, passive movements of the body at various angles in the vertical plane could not be carried out. We confined our observations of eye position in this plane to patients placed in the prone position. Under these circumstances, in the majority of patients the eyes move from their previous upward deviation into the midline or below it and remain there as long as the prone position is maintained. In some cases this reaction may not occur ; apparently the retroflexion of the head which keeps the eyes in upward deviation counteracts the opposite effect upon the eye position brought about by the prone position of the body, a counter-effect which can be more or less powerful. The reactions are similar when, as in the delayed fits, head and eyes are deviated to one side at the very start of the convulsion ; the eyes will move appropriately into the midline or to the opposite lateral position, according to the passive movements of the head. It is possible to maintain the eyes in the midline if the head is prevented from moving into tonic lateral deviation.

In the clonic phase, where the eye and head posture is little different from that of the tonic phase, passive alterations of head and body position have the same influence upon the eyes. The reaction is often much less marked during the last few clonic spasms, and it is as a rule identical with the reaction obtained in the beginning of the post-convulsive stages.

In the post-convulsive stage the eyes deviate laterally and upward with the head still retroflexed and with definite moderate contraction in the extensor muscle group of the head ; passive lateral movements of the head can be carried out without resistance. Less frequently, from the start of the post-convulsive phase the deviation of the eyes is lateralward without retroflexion

of the head. In this period often only slight ipsilateral movements are observed when the head is passively turned or rotated ; the reflex movement of the eyes is more extensive when the whole body is turned to one side. After a short time the eyes can be moved by neck and body posture reflexes, and fixed at any point of the orbit as freely as in the tonic or the greater part of the clonic phase. In the late post-convulsive stage, when inco-ordinated, jerky, pseudo-spontaneous movements of the body set in, the reflexes are still obtainable, though more difficult to observe and not so regular. By electrical stimulation of the sternomastoid muscles, the consequent rotation of the head to one side causes the eyes to move to the same side ; if the head is prevented from moving whilst the muscle is contracting, the eyes remain fixed in their position. They return to their previous position when the head is passively turned to the mid-line, in spite of electrically-stimulated contraction of the muscle. In the post-convulsive phase, the upper eyelid participates in the downward movement of the eyes, which is elicited by ventroflexion of the head ; both of these movements are tonic, and can be reversed by retroflexion of the head. The lid phenomenon is probably a synergistic movement ; it does not appear in the tonic nor in the clonic phase, where the orbicularis oculi is in spasm.

No compensatory contralateral movements of the eyes were observed during the tonic or clonic phases, neither by slow nor by rapid passive movements of the head ; such contralateral movements were occasionally seen in the later stages of the post-convulsive phase, when it was found that the eyes first made a contralateral movement but followed immediately the direction to which the head was turned.

In a number of cases syringing of the ears with cold water (10 c.c.) was carried out in the various phases of the seizure. The result was the same as reported by Hemphill (1940), who carried out the syringing during the various stages of the fit. When the reflexes here described were present, the labyrinthine stimulation with cold water elicited an ipsilateral deviation of the eyes with abolition of the quick nystagmus component. When observed throughout the post-convulsive phase the eye deviation elicited by syringing can be altered and ipsilaterally directed by passive alterations of head posture. When jerky movements have set in, the deviation of the eyes produced by cold water stimulation becomes less or disappears. Instead, both slow and quick nystagmus components appear, whilst simultaneously alterations of the head posture cease to influence the eye position.

Discussion.

We have observed :

(1) A tonic response of the eyes by alteration of the postures of the head relative to the body—obviously a tonic neck reflex ; according to Magnus, the afferent impulses enter the first three posterior cervical roots, and the reflex centre lies in the uppermost cervical segments ; the path conducting the impulses from there to the eye muscles is not known.

(2) Tonic reflexes with vertical deviation of the eyes, by alteration of body posture, with the head fixed, in the vertical plane, which represent tonic

labyrinthine reflexes ; they were thought to be caused by the otoliths exerting a pressure or traction upon the maculae, according to the position of the head in space (Magnus, 1924). This opinion has not been corroborated by more recent experimental work, and the exact site of origin of these reflexes within the labyrinth is uncertain (de Kleyn and Verstegh, 1933 ; Hasegawa, (1931 ; Tait and McNally, 1934–5).

(3) A horizontal tonic eye deviation by alteration of the posture of the body in the horizontal plane ; neither in experimental nor in human pathology has this alteration in body posture been seen to elicit any kind of postural reflexes ; but we may assume that these reflexes are also mediated through the labyrinth.

Tonic neck and labyrinthine reflexes upon the eyes are well marked in animals with lateral position of the eyes, and have been analysed in detail by Magnus (1924) in his work on positional reflexes. They are compensatory in character, i.e. opposite to the direction to which head or body is moved. In higher animals and humans, with frontal position of the eyes, these compensatory eye deviations are rudimentary. It is assumed that rotation of the head evokes a stimulation of the semicircular canal and causes deviation of the eyes, and that under the influence of neck or labyrinthine reflexes this deviation becomes fixed. This opinion, however, is not generally accepted. Bielschowsky is of the opinion that only the compensatory movements obtained by rapid rotation of the head are of labyrinthine origin, and that the same eye movements caused by slow rotation of the head are optic reflexes. Ipsilateral tonic eye deviations do not occur under normal conditions of the nervous system. There are a few observations under pathological and experimental conditions. Holmes (1938) found compensatory movements in lesions which caused deviation of the eyes by passive turning of the head ; sometimes they were also present when the eyes were closed. Holmes (1938) stresses, as did Bielschowsky, the importance of the optic factor in the compensatory eye movements, especially that of fixation, but he does not exclude a labyrinthine component. He does not mention whether the compensatory eye movements in his cases were of tonic character. Apart from electric shock treatment, we have observed lately four cases of deviation of the eyes, with special attention to the neck reflexes. In the first case there was a permanent deviation of the eyes for several days, accompanied by a slight deviation of the head ; the active movement of the eyes to the opposite direction was absent ; the symptomatology pointed to a subcortical lesion damaging the frontopontine oculomotor fibres. In the second case there was a similar permanent deviation of the eyes ; the active movements to the opposite direction were reduced to guiding movements ; small scattered cortical haemorrhages were found, the most extensive being in the lower third of the posterior central and the bordering supramarginal gyrus. The other two were cases of Jacksonian seizures ; the seizures appeared at short intervals, and we had the opportunity of observing a great number of them ; one case presented deviation of the head and eyes, the other deviation of eyes alone. In none of these cases were we able to change the position of the eyes by passive movements of the head during the seizure. In experimental work on monkeys under mild anaesthesia Graham Brown (1922)

found compensatory movements of the eyes by passive change of the position of the head, and he was able to influence this deviation by simultaneous electrical stimulation of the cortical oculomotor area. He does not mention whether the character of the eye deviation was tonic, and Magnus (1924) assumes in the discussion of these experiments that the deviation was merely the reaction to rotation. There are few reports of tonic neck reflexes eliciting ipsilateral deviation of the eyes. In immature and newborn children in the first two days after birth, Barany found that when the head was fixed and the body turned through an angle of not less than 90 degrees, the eyes deviated to the side to which the turning took place ; they remained deviated as long as this posture of the body was maintained. Magnus (1924) reports a case of a tumour in a child (details of the case are not given) in which ipsilateral eye deviation upon tonic neck reflexes was obtained. In the same monograph Magnus reports experiments on two monkeys who showed tonic neck reflexes with ipsilateral movements of eyes after removal of the cortex with preservation of the thalamus. Tonic labyrinthine reflexes with horizontal eye movements, i.e. horizontal deviation of the eye by movement of the body in space, have not been observed.

In the attempt to correlate the literature with our observations, we will first consider the relation of the direction of eye deviation to alterations of head and body posture. The contrast in the direction of the eye deviation is especially striking where a compensatory deviation in the pre-convulsive phase reverses quite abruptly into an ipsilateral deviation in the tonic phase, following the same alterations in head posture. It is unlikely that such opposite reactions should take place in consequence of the same mechanism. This sudden reversal must be related to a change in the mechanism involved. There is a difference in the character of the gaze ; during the preconvulsive phase, in which the compensatory eye movements were observed, the gaze was fixed and rigid, while in the following tonic and clonic phases, in which the ipsilateral eye deviation appeared, the gaze seemed to be empty and undirected. This fixed position during the preconvulsive phase does not arise as a consequence of body or head posture, in contrast to the eye position in the following stage. This suggests a mechanism for the compensatory eye movements arising primarily in oculomotor centres rather than in the labyrinth ; a rigid fixation of cortical or subcortical origin may play a decisive part, as Holmes assumes. Such a centrally-directed fixation does not necessarily mean a fixation on a definite object ; the fact that these compensatory eye movements may persist with the eyes closed is not inconsistent with a central origin.

The ipsilateral deviation of the eyes, observed almost throughout the epileptic seizure, is certainly due to tonic neck reflexes. These reflexes have not been found under normal conditions, nor have they been obtained in local cortical discharge, which leads to deviation of eyes and head. We have elicited them only as long as voluntary active movements of the eyes were absent, and the observations by Barany (1918) of tonic neck reflexes in the first days after birth emphasize the significance of this point, as it is known that fixation and voluntary movements of the eyes are not present at this period. These facts indicate that the release from higher oculomotor centres is one of

the fundamental conditions for the appearance of these reflexes. They are of the same order as the tonic neck and labyrinthine reflexes upon the limbs, which are known to be especially marked in release at brain-stem level, as in decerebrate rigidity.

The release of the oculomotor brain-stem centres has its peculiar features ; according to the findings in the release syndrome in other muscle groups of the body, an increase in eye muscular tone would be expected. Holmes (1938) has emphasized the rigidity of the eye muscles in defects of eye movements caused by pseudo-bulbar paralysis, under conditions where the oculo-motor brain-stem centres are more or less isolated. We found no indications of an increased eye muscle tone during the convulsions, apart from a short period in the post-convulsive phase. On the contrary, the reflex as well as the spontaneous reactions of the eye muscles suggest a diminution of tone ; during the convulsions the slightest positional alteration of head or body will direct the eye position, and in the post-convulsive phase the eyes are seen to float from one side to the other without being able to maintain a stable position. The only sources of tone for the eye muscles and for the regulation of their movements under the condition of epileptic coma seem to arise from neck and labyrinthine reflexes.

In a number of observations there is a short period at the beginning of the post-convulsive phase in which a lateral eye deviation occurs independent of head and body posture, and in which the tonic reflexes upon the eyes are less effective ; as this is followed by the re-appearance of very marked tonic reflexes, a central causation of this transitory condition is unlikely. There is no special alteration in the condition of the body muscles coinciding with this change in the reactions of the eye muscles ; possibly there is a connection with the clonic contractions which precede this phase, the convulsive movements may cause an excitation in the labyrinthine system, and a difference in the intensity of the excitation between each side could account for the deviation.

During the convulsions and in the post-convulsive phase, when the tonic neck and labyrinthine reflexes are obtainable, syringing of the ears with cold water is followed by ipsilateral deviation of the eyes. A similar reaction has been found by Rosenfeld (1910/11) and others in patients under moderate anaesthesia, with corneal and pupillary reaction present. Tonic neck and labyrinthine reflexes are not mentioned in these investigations. Rosenfeld found also that when the comatose condition becomes deeper the vestibular reactions upon the eyes disappear. We have not examined cases in moderate anaesthesia, but we examined a number of patients in fairly deep coma under various pathological conditions, and found, in agreement with Rosenfeld, that there was either no response following syringing with cold water, or very slight response when the stimulus was increased ; tonic neck and labyrinthine reflexes were absent, as were all compensatory eye movements. In most of these cases the corneal reflexes were present, the pupils were contracted, and showed a very slight light reaction or none at all. Preliminary investigations on patients undergoing insulin treatment show that during the insulin coma, when the corneal and light reflexes are still present, the same combination as in the electrically-produced epileptic seizure is found ; ipsilateral tonic neck

and labyrinthine reflexes upon the eyes can be elicited and syringing with cold water make the eyes deviate to the ipsilateral side. The site of origin of the quick nystagmus component has been the object of numerous experimental investigations. It has been demonstrated in animal experiments that the quick component could still be elicited by vestibular stimulation when the brain had been removed down to midbrain level. According to Spiegel and Sommer (1944), the vestibular nuclei are the site of origin of both nystagmus components, the excitation being conducted to the eye muscles by way of the posterior longitudinal bundle and reticulate substance. On this basis the abolition of the quick nystagmus component in comatose patients is difficult to explain. Magnus considers that functional damage to the eye muscles may be accountable, but this is not satisfactory, as it is not borne out by clinical experience of such lesions. In our observations, deviation of the eyes and abolition of the quick component can occur in the presence of active light and corneal reflexes; when related to the above experimental results, this would mean that a selective functional damage had been done to formations at a low brain-stem level, whilst those at a higher level remained intact. Experiments of one-sided decortication, however, show that the cortex, i.e. the corticofugal pathways, has a definite influence upon the quick nystagmus component (Bauer and Leidler, 1911; Dusser de Barenne and de Kleyn, 1923; and de Kleyn and Verstegh, 1927). Moreover, experimental results on animals cannot be applied without reservation to human conditions.

The literature is contradictory on this subject. The following facts are significant: In certain comatose conditions (electric shock, epileptic seizures, insulin coma) and in premature children, ipsilateral deviation of the eyes (with abolition of the quick nystagmus component) can be produced by cold water stimulation and by tonic neck and labyrinthine reflexes. In the post-convulsive phase of the electrically-produced seizure, the eyes deviate upon syringing as long as tonic neck reflexes upon the eyes can be obtained; these disappear with the reappearance of innervating impulses, when the quick nystagmus component again becomes manifest. This suggests a pathophysiology common to both mechanisms; loss of voluntary eye movements and central muscular tone—signs of an isolation of oculomotor brain-stem centres—which are the main factors for the appearance of tonic neck and labyrinthine reflexes, may also be essential for eye deviation upon external stimulation. The eye movements have thus come under the exclusive control of primitive reflex mechanisms whose response is retricted to adversive movements.

Recently there is the tendency to move the site of origin of the epileptic mechanism from the cortex toward the brain-stem (Delay, 1946, and other authors), but definite facts for an unequivocal answer are lacking. Experiences on cortical stimulation still form the main basis for the interpretation of the pathophysiology of eye position and movements during the epileptic fit. Following his observations on electrical stimulation of the cortex, Foerster (1936) is of the opinion that the tonic mass movements, including the adversive movements of head, eye and body in the epileptic fit, have their origin in the extra-pyramidal cortical area (6αβ area of Vogt). Penfield (1939, 1941), whose experiences differ somewhat from those of Foerster, concludes that head or

head and eye turning has a lower representation and occurs in the epileptic seizure when the discharge extends into the subcortical (extrapyramidal) centres. No turning of the head takes place when the discharge spreads rapidly into the subcortical extrapyramidal centres of both hemispheres, because the effects of both sides are then balanced. He is of the opinion that the frequency of upward deviation in epileptic seizures may be related to the frequency of upward deviation of the eyes obtained by frontal stimulation (areas $8\alpha\beta\gamma$ of Vogt). Some of Penfield's conclusions approximate to those of Muskens, who refers the conjugated oculomotor movements to subcortical extra-pyramidal centres. But these authors apparently agree that deviation of eyes and head during the generalized fit are co-ordinated movements, and due to discharge.

Our investigations show that neither of these conclusions is true in electrically-produced convulsions. In localized seizures of Jacksonian type due to focal cortical lesions, with co-ordinated deviation of head and eyes or with isolated deviation of the eyes, no tonic neck or labyrinthine reflexes upon the eyes can be obtained. The mechanism is quite different in generalized fits due to electric shock, where the eye position and deviation throughout the epileptic spasm is determined by tonic reflexes from the neck muscles. Upward deviation of the eyes, common in the electrically-produced fits, as in spontaneous generalized epileptic seizures, is thus explained as a tonic neck reflex, elicited by the preceding retroflexion of the head. The presence of tonic neck reflexes from the very start of the convulsions suggests the rapid onset of a low subcortical release mechanism.

Summary.

Tonic neck and labyrinthine reflexes during electrically-produced seizures are described. They lead to ipsilateral deviation according to the posture of head and body. Ventroflexion of the head causes downward deviation of the eyes; retroflexion of the head causes upward deviation. The upward deviation of the eyes commonly seen during the tonic phase is conditioned by the preceding retroflexion of the head. The primitive pattern of ipsilateral eye deviation has also been obtained by stimulation of the labyrinth with cold water. The physiology of these reactions has been discussed. The fact that these reflexes are manifest at the onset of the seizure suggests a sudden release of oculomotor brain-stem centres by the epileptic fit.

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PERIODIC CATATONIA.

By J. S. Bonar Lindsay, M.B., Ch.B.(N.Z.).
(From the Division of Mental Hygiene, Health Department, N.Z.)

Kraepelin (10) in 1908 first defined a group within his classification of schizophrenia which he described as periodic catatonia. The clinical features of this type may be briefly summarized. The onset, usually between 14 and 20 years, is frequently characterized by a period of erratic conduct followed by an interval of stupor, confusion or excitement, which thereafter undergoes periodic remissions and relapses. The periodicity is remarkable in the rapidity with which all changes occur. In the periods of remission the patient is free of catatonia and associated symptom-complex (sympatheticotonia), but is still dull, apathetic and withdrawn; he often recalls events from the reactive phase, but without insight. The patient is still schizophrenic, with emotional flattening and poverty of ideation, and remains so throughout. In the reactive phase the picture is one of catatonic stupor or excitement, with clinical evidence of sympathetic over-activity.

The most clearly defined cases are those in which there is a synchronicity in catatonia and sympathetic function; in these the change in state is more rapid, the catatonia more profound. Gjessing (7) calls these the synchronous-syntonic group. Other less typical cases are described as asynchronous-asyntonic. The sympathetic changes synchronous with the onset of catatonia are those of adrenal-orthosympathetic over-activity. Increases in the pulse from 70 to 100–120 occur in a few hours. The blood pressure may likewise increase by over 40 mm. Hg. There is pallor, cold clammy extremities, mydriasis, fleeting anisocoria, and, during stupor, a fine tremor and retention of urine. Even when the patient is immobile night and day there is an increase in B.M.R. Urinary output and weight decrease and the viscosity of the blood increases.

Gjessing (7) has studied this group of patients, recording many variables and body-constants over 3,500 "patient-days." He charted the following: psychic state, urinary output, specific gravity and constituents (ammonia, titratable acidity, chlorides, phosphates, indican, sulphate, and nitrogen output), oxygen intake, carbon dioxide excretion, respiratory quotient, alkali reserve, haemoglobin, white cell count, blood sugar, plasma nitrogen, body temperature, weight, and pulse rate. He also made estimations of the nitrogen balance.

As a result of this momentous amount of work, a relationship has been established between the nitrogen balance and the periodicity. This further resolves itself into two types which Gjessing calls types A and C. In type A the patient increases his nitrogen store to a peak, and shortly after excretion starts, catatonia develops, only to disappear when the store has been eliminated. In type C the catatonia starts at the end of the period of excretion and persists

throughout the building up of the store of nitrogen. Gjessing was also able to demonstrate that the electrocardiogram shows a flat T1 during nitrogen retention irrespective of the mental state. The non-protein nitrogen in the blood follows the nitrogen periodicity. A rise in the blood sugar is seen in both types at the onset of the catatonia and orthosympathetic phenomena, but in type C the level remains above normal in the quiescent periods, in type A below normal.

It can be seen from a study of type C that the increased metabolism of the reactive phase is not the cause of the nitrogen swings, for here there is retention during activity. Stokes (16) has reported a case with characteristic metabolic studies in which later it was possible to demonstrate periodic catatonia, not with phasic changes, but with a steady accumulation of nitrogen.

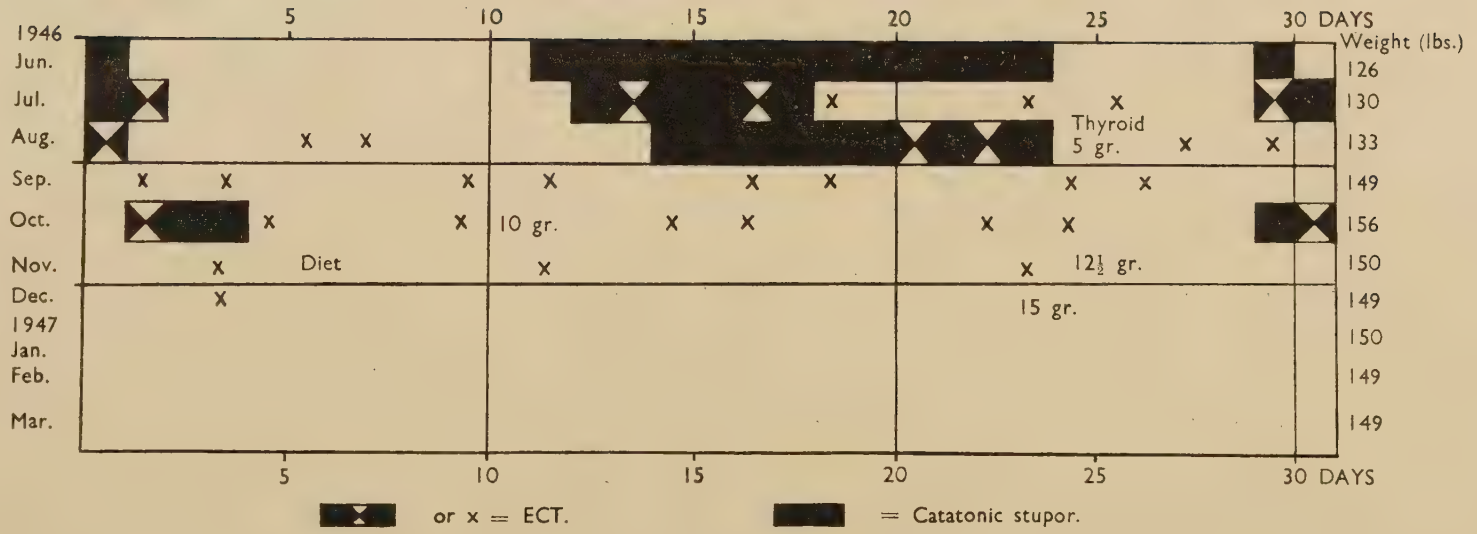
It may be stated, therefore, that in periodic catatonia the mental state is not the direct cause of the known biochemical changes, nor are the latter the immediate cause of the former.

The two cases that are reported below have been studied over a long period. Only one body constant has been recorded, that of body weight. As this may reflect the total metabolism of the individual better than a record of the individual parts thereof, it may be deemed relevant to the study of periodic catatonia.

Case 1.—The patient was born in 1919. His father died of melancholia in 1928. His earlier life can be briefly summarized as follows. He attended school till 15 years old, with two years' post-primary education. The subsequent year he spent as an office boy, and during the next year he had three jobs. During this period he became progressively more retiring, self-conscious and "absent minded," and often day-dreaming.

He was first admitted in July, 1936, after three weeks' excited schizophrenic behaviour. During the first two months he showed two periods of excitement with fairly rapid onset. He asserted that he was Edward VIII, and that he was to marry his sister, and make her Queen of England. This fluctuating course persisted for eight months, with his weight varying from 9 st. 7 lb. to 8 st. 6 lb. His weight then increased to 11 st. 5 lb. and at the same time his mental state improved, so that after five months in a parole villa he was released on probation and later discharged recovered.

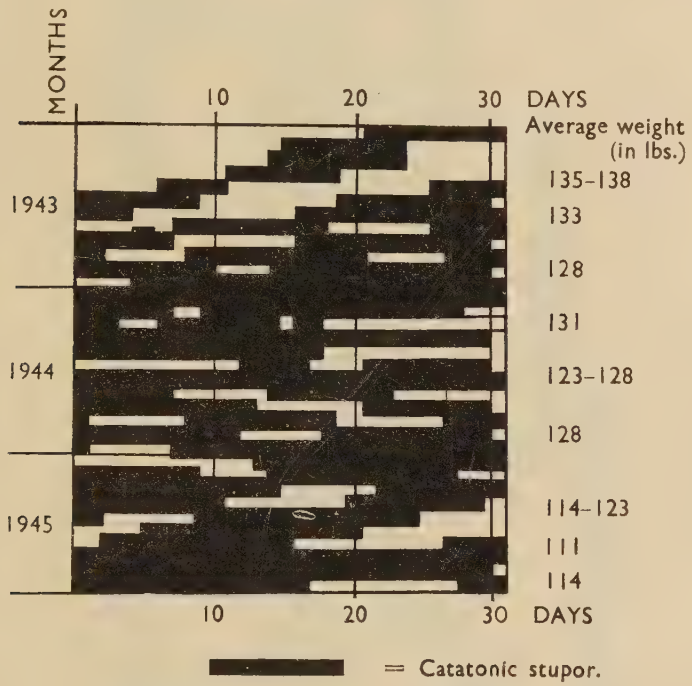
For nearly two years after his release he worked in the country. In July, 1939, he was arrested for petty theft and readmitted. For four months he was periodically restless, noisy, erratic, and abusive, with at times signs of the catatonic stupor, later so pronounced. During this four months his weight rose from 9 st. 8 lb. to 11 st. 6 lb. At this stage he again improved, and after 8 months was discharged recovered. The record of his weight is of interest at this period. One month before his discharge his weight was 12 st. 4 lb., at the time of his discharge 11 st. 2 lb. Three days later he returned for admission as a voluntary boarder as a precautionary measure on account of some restlessness. His weight was 10 st. 13 lb. He relapsed and showed periodic catatonic behaviour a week later. He was formally committed three months later after he attempted to commit suicide, prompted by the bad thought he got from the Devil. For two years (1941 and 1942) he showed a continuation of the periodicity of catatonic phenomena, with quiescent intervals during which he was well enough mentally to work with a party. His weight through these two years varied from 9 st. 6 lb. to 10 st. 11 lb. The next three years showed a progressive worsening in the degree and length of the stupors. In the quiescent periods he was dull, apathetic and indifferent, but able to do routine tasks under supervision and care for person and clothes. In a stupor he lay curled up, immobile, mute, indifferent to personal habits and resisting all attention. The maximum recorded weights over these three years are 9 st. 12 lb., 9 st. 5 lb., 8 st. 11 lb., and correspond to the progressive increase in length and depth of stupor.



CASE 1.—Diagrammatic representation of the progress of treatment.

The minimum weight recorded was in June, 1945, 7 st. 13 lb., near the onset of the longest stupor recorded in his files—78 days. Towards the end of this stupor the toes showed marked " Raynaud's " phenomena, which progressed till they were nearly gangrenous. With the termination of the stupor these improved spontaneously. This observation was presumed to be an index of the intensity of the orthosympathetic over-activity. The pulse rate was frequently up to 130 in a stupor and between 70 and 82 in quiescent phase. Axillary temperatures were recorded up to 99·2° F. in a stupor.

After several more stupors in 1946 of up to 20 days' duration, with a body weight between 8 st. 4 lb. and 9 st. 2 lb., active treatment was instituted in July, 1946. E.C.T. was first given. Resulting from this was an increase in weight over two months of 7 lb. Stupors appeared to recur, but each recurrence remitted after

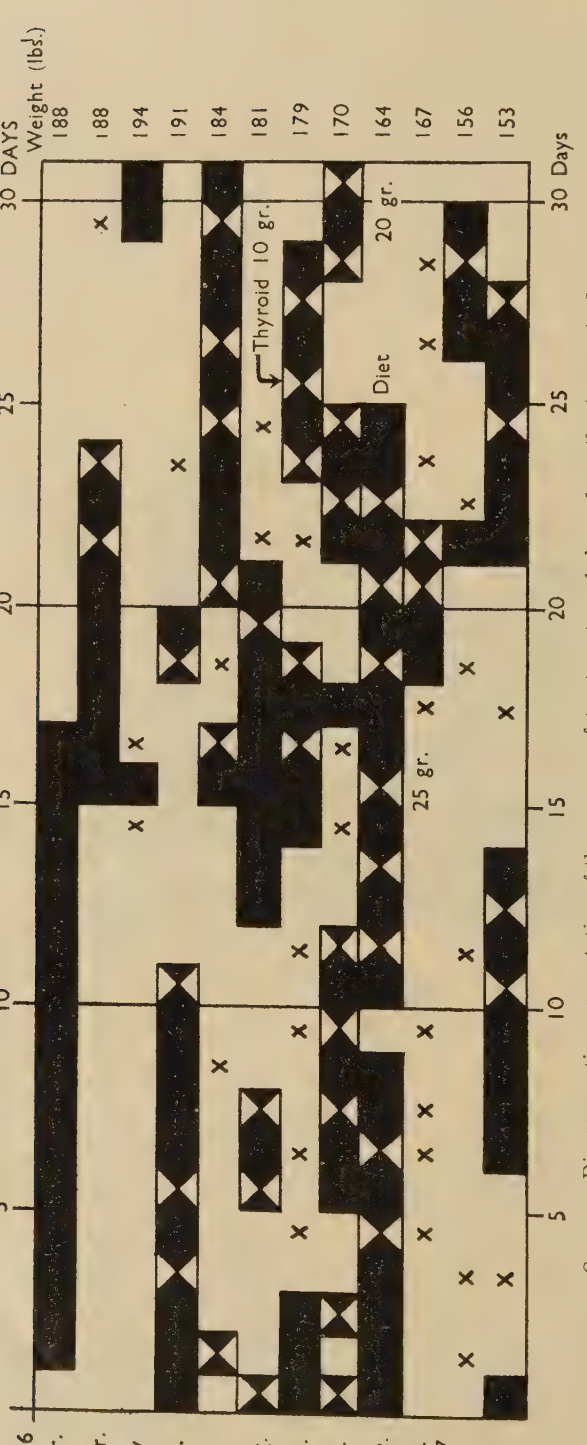


Case 1.—Periodicity of the catatonic stupor for 34 months (represented diagrammatically).

two E.C.T. In the next two months he was given thyroid extract (5 gr. per diem, increased to 10 gr. after six weeks), with also approximately the same number of E.C.T. as in the previous two months. His weight increased by 23 lb. in the two months and he had only two short periods of stupor—five days in all. Body weight at the end of this two-month period was 11 st. 2 lb. He remained free of periodic catatonia.

Further treatment was continued. According to the recommendation of Gjessing, he received a low protein diet (qualitative). The thyroid extract was increased to 12½ gr., then 15 gr. per diem and the E.C.T. tapered off. In this quiescent phase the basal metabolic rate was — 7 per cent. on thyroid extract 15 gr. per day. With the increase in thyroid dosage his weight dropped to a steady level between 10 st. 5 lb. and 10 st. 9 lb. In the next six months he remained at a fair institutional level, he was still dull and apathetic, and still had nocturnal enureses. The thyroid dose remained at 15 gr./day and his weight 11 st. to 11 st. 8 lb.

Case 2.—This patient was born in 1902. Until 1937 he had an excellent record. He was a university graduate, and a good athlete, though shy in his manner and bearing. There was no family history of instability. The onset of the psychosis was sudden and he was admitted in April, 1937. When he was first examined



CASE 2.—Diagrammatic representation of the progress of treatment-symbols used are the same as in Case 1.

he was usually co-operative, though at times vague and hesitant. On other occasions his speech was rambling, with intervals of silence, loss of train of thoughts and tears for no apparent reason.

" It's dawning on me now, I'm St. John, John of Runnymede, King John. . . . It's being revealed to me I'm Sir Percival, the knight who saw the Holy

Case 2.—Periodicity of the catatonic stupor for 72 months diagrammatically represented.

Grail. . . . You're the fellow—, the engineer, I'm the protector of the poor and I've been betrayed. . . . No! I haven't been betrayed." He denied hallucination, but stated " It's all within me." This type of conversation and his schizophrenic behaviour has persisted in his quiescent phases ever since.

Shortly after admission he became restless, more confused, fragmentary in speech, and neglected his bodily habits. He rapidly changed into a marked catatonic stupor, lying curled up on his back, staring at the ceiling for hours with negativistic and impulsive behaviour if disturbed. This period of catatonia remitted, but was followed by another in three weeks. In this second stupor he had to be cathe-

terized for retention. For the next eight years and six months the periodicity of the catatonia was regular, and in this period of 102 months he had 116 periods of stupor. The duration, sequences, and body weights over six years can be seen in the graph.

In January, 1946, he was subjected to a full investigation of his urinary tract following further episodes of retention. No lesion was found, nor would such be likely to be found if the retention were due to orthosympathetic over-action as postulated. In the next three months he had three periods of stupor of 12 to 14 days' duration, with a sequence similar to those immediately preceding it. In the catatonic phase the pulse varied from 96 to 118 and the axillary temperature reached as high as 99·4° F. In the quiescent phase the pulse was recorded between 70 and 80.

E.C.T. was started in April, 1946, and after an initial favourable response (the predicted stupor was represented by one day of erratic conduct) associated with a gain in weight of 6 lb. he relapsed. For the next four months the stupors recurred more frequently, but each could usually be interrupted by two or three E.C.T. The weight dropped 15 lb. Thyroid administration was then started (10 gr. per diem of thyroid extract), and this made the situation worse. The stupors remained as frequent, but no longer responded to E.C.T., so that he had six stupors in eight weeks with only 14 days in the quiescent phases. His weight dropped in this two-month period a further 15 lb.

Temporary success was gained by increasing the thyroid extract to 20 gr. and then 25 gr. per diem. He had one four-day stupor in 54 days. His weight did not fall, though he was for this period on a low protein diet (qualitative). Regular E.C.T. was continued once or twice a week.

A relapse followed, associated with another fall in weight of 13 lb. He changed little in the next six months. Weekly or fortnightly E.C.T. was continued to interrupt the stupors. Their frequency was thus still increased. The body weight remained at 12 st. 6 lb. approximately for most of this period. Thyroid was discontinued after the period recorded in the graph.

Comment.

These two cases represent examples of the least common type of periodic catatonia. Two-thirds of the cases are females and excitement is commoner than stupor.

The course of the illness in these two patients is different. Cases with a clockwork regularity over decades are recognized, and others with progressive intensity of the syndrome over years with or without remissions are also identified.

The first case conforms to all the criteria, including the therapeutic test with thyroid for periodic catatonia. Apart from the therapeutic failure in the second case it likewise appears to be indubitably a case of periodic catatonia. The fact that the underlying process is schizophrenic is well shown in the second case with manifest schizophrenic symptoms present in all the quiescent phases.

It has been possible to follow the body weights of these two patients over the period of illness and the variations have been recorded. The first case shows several facts of interest. The patient has never been free of catatonic behaviour of a periodic nature with a body weight of less than 11 stone (approximately) before treatment. With thyroid he achieved this at a level of $10\frac{1}{2}$ st. The lower his weight has been, the longer have been the periods of catatonia, and *vice versa*. His most profound stupor was associated with the most marked sympathetic phenomena. In the second case some less marked correlation appears to exist between the body weight and the length of the stupor. The

observation of interest in this case is in the therapeutic failure. The patient over four months with E.C.T. alone lost 15 lb., in the next two months with thyroid and E.C.T. another 15 lb. The catatonia was worse. The first patient gained 7 and 23 lb. on a similar sequence, and was free of catatonic behaviour.

Studying this body weight constant in the reported cases, there appears to be a relationship between body weight and the symptoms. Periodic catatonia does not remit unless there is a gain in weight. Gjessing's (7) case C. J. L— shows a more frequent and longer catatonia with a lower body weight. Stokes' (16) case shows similar changes : thus the ratio between duration of catatonia to quiescent phase was 2 to 1, with the weight between 8 to 9 stone, but between 9 st. to 9½ st. the ratio was 6 to 5. These figures are only approximations in view of the small scale of the reproduced graphs. Later phases in Stokes' case appeared to have an ill-defined end to the catatonic phases with the weight over 10 st., suggesting a further lessening of the degree of stupor. There is no doubt that gross anatomical lesions of the hypothalamic nuclei can result in alterations in weight and metabolism. The body weight has been used tentatively as an index of the ability of the hypothalamic centres to control a normal internal environment.

Discussion.

Much suggestive work has been done that throws light on the synchronous catatonic orthosympathetic phenomena. De Jong (5), after many experimental studies, considers that catatonia is a "general" reaction form of the C.N.S. which, like symptomatic epilepsy, may have many causes, and likewise represents a non-localized motor discharge syndrome of the C.N.S. The sympathetic phenomena accompanying catatonia he attributes to the overdischarge of the centres. Experimental lesions in the posterior hypothalamus have produced hypokinesis and akinesis, and Bailey (2) has demonstrated a cataleptic element with these lesions. On the other hand, cortical stimulation is facilitated by simultaneous hypothalamic stimulation. Affective (rage) reactions are demonstrated in stimulation of the intermediate zone, and orthosympathetic overactivity dominates from posterior hypothalamic lesions. Similar reactions are induced in decorticate animals from very ordinary stimulation. Cairns (4) has reported a case of third ventricular cyst with akinesis and mutism. Likewise Furtado (6) has noted a similarly placed cyst with catatonia. A case of pituitary cachexia with catatonia was recorded by Stocks (15). Cases of hypothalamic lesions with excitement have been reviewed by Alpers (1). A few reports are available dealing with paroxysmal autonomic discharges, either as a diencephalic autonomic epilepsy (Penfield (13)) or post-encephalitic autonomic crises (Oller (11), Ostow (12)). The case reported by Ostow (12) showed post-encephalitic crises with cataleptic manifestations, such as akinesia, rigidity, and mutism, with concomitant autonomic reactions consisting of diaphoresis, rapid pulse, fever and hypertension. Oller's (11) case showed hyperkinetic reactions and aggressiveness, associated with an autonomic discharge. Thus the clinical picture is like the periodic catatonia-orthosympa-

theticotonia of periodic catatonics, apart from the time course of the disturbance. This difference can be correlated with the fundamental disease-process responsible for the discharge. In post-encephalitic states episodic manifestations are common, and are comparable in duration with the disturbances in the cases quoted. The relationship of periodic catatonia to schizophrenia is discussed later.

It is in catatonic schizophrenia particularly that physical signs are most evident. These signs are of sympathetic nervous function disorder and are not those of recognized endocrine disorders. On the other hand, paranoid states with a paucity of such signs show a relatively high incidence of endocrine tumours at autopsy (Pollak (14)). From these considerations it is suggested that the catatonic sympathetic phenomena of catatonic schizophrenia are a definite somatic syndrome associated with schizophrenia, and that this syndrome is a reaction pattern of the C.N.S., probably hypothalamic in origin. The possible significance of the fact that the sympathetic phenomena appear synchronously and in a pure culture of orthosympathetic overactivity in periodic catatonia will be examined later.

The other *sine qua non* of periodic catatonia is the basic schizophrenic illness. In the quiescent periods the schizophrenic nature is usually apparent. In the reactive phases they are obvious catatonic schizophrenics. Referring briefly to the two reported cases, it is suggested that the difference in the course between the two is related to the degree of the basic schizophrenia. The first case with remissions showed only mild symptoms during the quiet phase, but the second with a relentless periodic course was markedly schizophrenic. Further life history studies of these patients are required to confirm or refute this suggestion.

Following Stokes' (16) demonstration that the periodicity could continue without phasic nitrogen swings it becomes necessary to classify this latter with other secondary phenomena. The treatment for periodic catatonia advocated by Gjessing (7) is the administration of thyroid hormone. This was devised to eliminate the nitrogen storage. The pharmacological response following thyroid administration is an increase in metabolic rate. A decrease in body weight and elimination of nitrogen are probably secondary results of this increase. The marked increase in body weight that follows thyroid administration in periodic catatonia (favourable response only—Case 1) is difficult to fit into accepted ideas. It would seem more logical, however, to explain the therapeutic response in terms of the more fundamental action. In the two cases reported, the favourable response to treatment only occurred in the case with a weight increase during thyroid administration. It is suggested that a thyroid-hypothalamus interrelationship is involved and that, as the hypothalamic control of the internal environment improves, in a favourably responding case, the body weight is approximated to the mean for height and build.

Theories to date to explain the nature of the illness appear to be two in number. The intoxication hypothesis, particularly amine intoxication, has been repeatedly suggested as a cause of many types of mental illness, and Gjessing (7) suggested it as a possibility in periodic catatonia.

The weight of evidence is against any such amine intoxication hypothesis, even though certain amines can cause mental symptoms, catatonia and sympathicomimetic changes, e.g. 3-4-5-trimethoxy or 3-4-dimethoxy derivatives of phenylethylamine. It has also been shown that some secondary carbinamines inhibit brain respiration in dilutions approaching *in vivo*. Jantz (9) has shown that metabolic changes can occur after 3-4-5-trimethoxy-phenylethylamine similar to those in schizophrenia. Stokes (16) has shown in his reported case periodicity of mental state, at first synchronous with the phasic nitrogen changes, and then later independent of these metabolic changes. The nitrogen changes are not, therefore, the immediate cause of the mental changes. The changes reported are those of total protein metabolism and not just amine excretion. Gjessing (7) noted the occurrence of supernumerary phases after the thyroid administration had produced considerable nitrogen loss.

A second possible hypothesis is posed as a question by Stokes (17): "Is there a rhythmic upset of endocrine function more fundamental that the overt periodicity?" The overt periodicity is one of central autonomic regulation and catatonia. It is unlikely that there is a more fundamental rhythm than the central autonomic cycles except from higher centres controlling the hypothalamus.

It is proposed to examine the periodicity of central autonomic regulation in more detail, but before so doing it is advisable to note briefly some observations on the maintenance of homeostasis in schizophrenia.

Hoskins (8) and co-workers have studied over years many body constants and variables in schizophrenia. They come to the following conclusions: The functional level of some body constants is set at a lower level than normal. Subject to external influences (e.g. metabolic stimulants) these levels show lesser responses than normals. Despite this, however, the range over which they function in maintaining homeostasis is greater than normal. The "physiological withdrawal" of schizophrenics (decreased response to external factors) is associated with a decreased stability of the control of the internal environment. In periodic catatonia there is an increased lability in the control of various body constants. It might be deduced that such defective control would tend to magnify the amplitude of the phases of nitrogen balance. Also, studies of the nitrogen balance in normals, for example with menstrual cycles, would show a lesser variation than periodic catatonia. Quantitative data on the premenstrual nitrogen retention do not appear to be available in this country.

To provide a hypothesis for an illness with a periodic course it is necessary to consider the mechanism both for the onset and for the remission.

The only features that clearly separate periodic catatonia from catatonic schizophrenia are the orthosympathetic phenomena and the periodicity. They are otherwise clinically indistinguishable. Therefore if some characteristic mechanism can be formulated to explain the remissions, it would be reasonable to attribute the onset of periodic catatonia to the factors concerned in the genesis of the catatonia in non-periodic cases. The invariable association of schizophrenia with both the periodic and non-periodic type suggests an explanation of the onset.

In the studies of the onset of schizophrenia Boisen (3) and others distinguish three methods of reacting during the development of the psychosis—the drift into a psychotic state, the delusional misinterpretation, and the panic reaction. This third type is one in which "the individual is likely, in Malamud's phrase, to become aware that he is tasting forbidden fruit and to sense the danger in which he stands and to become fearful of it" (Hoskins (8)). The disturbances may take the form of either stuporousness or agitation. It is this type of reaction that occurs in patients later described as catatonic. To quote Hoskins further (8), "primarily his reaction seems to represent a manful if misguided attempt to solve his inner problems."

This type of panic onset can further be orientated into accepted neural mechanisms. The usual response to a "fear-panic" situation is one of orthosympathetic over-activity, with hyperkinetic, or akinetic and cataleptic patterns of motor activity. The peculiar nature of the pattern in a panic situation reflects the various past experiences, habits, and intelligence of the normal, whereas the kinetic quality of the response is the result of hypothalamic stimulation activity. Likewise, in catatonic schizophrenia, the detailed pattern of the catatonia reflects the disordered processes of the psychosis, whereas the quality of the kinetic element and the orthosympathetic over-activity are due to hypothalamic activity. As indicated above, the hypothalamic control in schizophrenia is more labile than in normals. Applying this concept to periodic catatonia, a most striking similarity is demonstrated in the intense orthosympathetic activity—an emergency or fear reaction in almost pure culture. As Gjessing (7) described, these phenomena are syntonic and synchronous with catatonia in periodic catatonia. The hypothalamic response is integrated towards one end. Thus it is assumed that if the hypothalamic response to a panic situation is integrated it produces some amelioration in the schizophrenia and a period of recovery from catatonia-orthosympatheticotonia. If the cause remains, i.e. the schizophrenia, relapses will occur. The liability to relapse will depend on the intensity and persistence of the schizophrenic process, and the stability of the level of homeostatic control. The more defective the homeostasis the more marked the periodic catatonia.

On the other hand, where the hypothalamic response is asyntonic—i.e. not integrated to one purpose—and asynchronous, periodicity, as such, is irregular, gradual in onset and remission, and may be absent over long periods.

The more common cases of catatonic schizophrenia with a very irregular time course show no co-ordination or integration of the hypothalamic response. Thus both orthosympathetic and parasympathetic over-activity may coexist and may bear no temporal or other relation with the kinetic variation. This failure of integration in a central nervous reaction leads to its persistence, in the asynchronous and asyntonic form. In the acute catatonic schizophrenic reactions, the favourable response is possibly due to remission of the basic acute schizophrenic reaction. In some cases it might be attributed to the integration of the panic reaction, which appears to be fairly definite, in many of these acute reactions.

Improvement in the schizophrenia is likewise absent with defective integration of this hypothalamic neural pattern. The periodic improvement of

the psychosis in periodic catatonia is of considerable interest, but it is not proposed to deal further with hypothetical aspects of the interrelationship between psychosis and hypothalamus, especially as regards E.C.T., insulin therapy and leucotomy. From a consideration of the therapeutic and spontaneous remissions it might be deduced that a possible mechanism for the remission would involve the increased metabolism of thyroid administration and orthosympatheticotonia respectively. Whether this is so or not, it would appear likely that the *locus operandi* is the hypothalamus.

It is necessary to examine the contributions of previous authors in terms of this hypothesis. If it is now applied to Gjessing's (7) types A and C it is possible that the following is valid. In type A where the periodic phenomena are most marked it is likely that the nitrogen balance will follow the periodicity in a uniform direction, i.e. almost co-temporaneously with the increased metabolism, the nitrogen balance will fall. In type C, with less intense periodic phenomena, it is possible that the reversal of nitrogen balance phases is an expression of the asynchronicity and asyntonicity, which in the common type of catatonic schizophrenic is a predominant feature in the somatic syndrome.

If the degree of disturbance of the control of homeostasis is reduced, improvement will result, but still dependent on the intensity of the schizophrenic process. With a normally controlled internal environment the body constants will tend to return to their mean range of values. At some stage of improvement it is suggested that some factors (such as nitrogen balance for example), which in marked disturbance follows the periodicity closely, may become divorced from this periodicity and move in a uniform direction towards a more stable and safe level (this is to explain Stokes's (16) case with catatonia and no nitrogen swings, but with increased body weight, and nitrogen accumulation).

Conclusion.

Briefly stated, the hypothesis here advanced states that the kinetic and sympathetic phenomena of catatonic schizophrenia are of hypothalamic origin. These phenomena are a specific neural reaction pattern to the " panic " onset of the psychosis. If this pattern is integrated it serves to restore the normality of the hypothalamic centres with some improvement in psychosis *eodem tempore*. This is the case in periodic catatonia. In non-periodic catatonia the specific hypothalamic pattern is disintegrated. The efficacy of the reaction depends on its degree of integration, on the degree of causal schizophrenia, and on the level of hypothalamic control of the internal environment at that particular time.

Summary.

1. A review of the condition of periodic catatonia is made.

2. Two cases are reported.

3. An analytical study is conducted into the nature of the symptoms of the disease.

4. A hypothesis is put forward about the nature of catatonia.

Acknowledgment.

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MISINTERPRETATION OF MIRROR IMAGE OF SELF IN PRESENILE CEREBRAL ATROPHY.

By R. E. Hemphill, M.A., M.D., D.P.M.,
Medical Superintendent, Bristol Mental Hospital.

Denial of knowledge of personal identity is occasionally encountered in various mental disorders. Temporarily present sometimes in hysteria, in schizophrenic psychoses it is expressed as a delusion that identity or name has been altered, and it may be a feature of the depersonalization syndrome. Seniles may maintain that they do not know or have forgotten who they are.

Although the question whether the ability to build up a body image and to identify self depends on impulses received from somatic and visceral structures is uncertain, normal individuals have a strong tendency to preserve the conception of self intact even after mutilation. The armless man does not regard himself as a different kind or new organism, but as the same being he formerly was, now deprived of the use, but not necessarily the existence, of an amputated member—a tendency well demonstrated by phantom limbs. The existence of individual members of the body is denied only in abnormal psychotic conditions and organic brain disorders.

The individual has an incomplete knowledge of his external appearance and patterns of shape and movement. He knows only what he has learnt from observing himself in a mirror or from photographs. This information is limited by physical factors, such as angle of vision, position of eyes, light, size of mirror, and flexibility of the body, so that it is practically impossible to recognize oneself from an unfamiliar angle—from the side or behind. The most important mirror image is the face—it is recognized easily, but the appearance of other parts of the body can seldom be recalled; thus, the hands, which one is accustomed to see directly from a certain viewpoint, look unreal in a mirror; while an unexpected encounter with oneself in a full-length mirror gives the impression of meeting a stranger.

The mirror image is an illusion in which the individual projects himself from without his body and accepts the reversal of right and left without difficulty. The marked difference between what an individual sees in the mirror and what others see of him is well demonstrated by self-portraits, which have a strange unreal quality, and are quite unlike portraits of others painted by the same artist.

To accept the mirror picture as a real image of oneself requires that certain conditions are automatically and unconsciously fulfilled: (1) The mirror must be accepted as a faithful instrument, and no doubt be entertained that

the person whose movements and dress are seen reflected is not really a stranger behind a glass who mimics every action. (2) The recollection of previous mirror pictures must be sufficiently clear to enable identification to be made immediately, irrespective of change of dress. (3) The mirror must be recognized as a reflecting instrument, so that a reflection is immediately identified as such. Failure to perceive that there is a mirror is the basis of many conjuring illusions, and there is no reason why a mirror image should be regarded as a personal reflection unless the mirror situation is comprehended.

It is therefore surprising that the literature contains almost no references to failure to identify oneself in a mirror after organic brain change, and, unless severe agnosia interferes with the recognition of the mirror as such, the mirror image is almost invariably correctly identified.

In the case reported below, not only was the patient unable to recognize herself in a mirror, but she contended, in all but experimental conditions, that what she saw was in fact her sister.

Case history.—A. C—, aged 62, married. Admitted June 2, 1942.

Family history.—There was a strong family history of insanity. Her mother became insane and died in a mental hospital in middle life, cause unknown. One sister died in a mental hospital, cause unknown. Another sister's son died in a mental hospital, aged 18, probably a schizophrenic. Another sister's son developed schizophrenia and is now in a mental hospital. Her father died of pneumonia, aged 64.

Patient's previous history.—Her childhood was normal. She was of average ability at school, and described as being always smiling and happy, capable and methodical. The home was comfortable and well kept. She was the youngest of a family of 2 sons and 5 daughters. Polly, the second eldest, was 18 years her senior. Polly did not marry, and kept house after the mother's death, bringing up the patient from the age of 4. At 24 the patient married. There were no children, the circumstances being poor. Her husband was a railway warehouseman, and she worked out as a daily domestic. Polly lived with her and her husband. These arrangements continued for 25 years. After the menopause at 50 the patient stayed at home. A slight intellectual defect became evident about this time, and she began to make mistakes in bills, and on this account gave up her work. By six years later, at 56, her memory was noticeably bad, but she was still able to do housework and some shopping. Four years later Polly died. Immediately the patient (then 60) became very much upset, so that she could not be permitted to go to the funeral. Thereafter she refused to admit that her sister was really dead and referred to her as a living person. She evidently missed her very much. A few days after the funeral she disappeared, and was discovered a week later 80 miles away, at Exeter, where she had spent her childhood. Apparently she had travelled by train and was found wandering, lost. She could give no account of her journey, but said she was looking for her sister. When she returned, her husband noticed that she did not appear to understand all that was said to her, and wondered if she had had a stroke. She would conceal an old framed photograph of herself, fearing it would be stolen, and at this time appeared to set some extraordinary value on it. Later it was demonstrated that she imagined it was a photograph of Polly. About the same time she would stand in her bedroom in front of a mirror gazing at the reflection, which she addressed as "Polly." She would spend hours in front of the mirror, and sometimes would wander from the house looking for her sister. When her husband moved the mirror she threatened to kill herself. Eventually she attempted to throw herself from a window, believing that her reflection in the glass was Polly outside. For this reason she was certified and admitted to the mental hospital, at the age of 62, two years after the death of her sister.

On admission.—Height 5 ft. 1 in. Weight 7 st. 11 lb. She was well covered and well preserved for her age, her arteries were soft, her heart normal, and her blood-

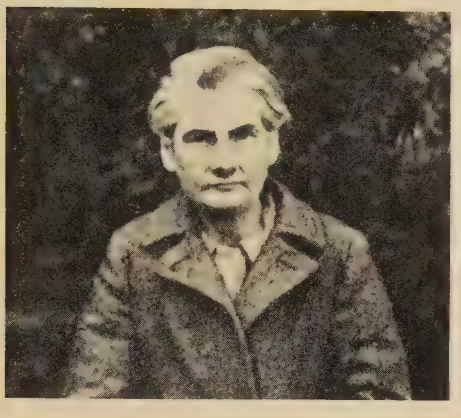

FIG. 1.—The patient, aged 62.

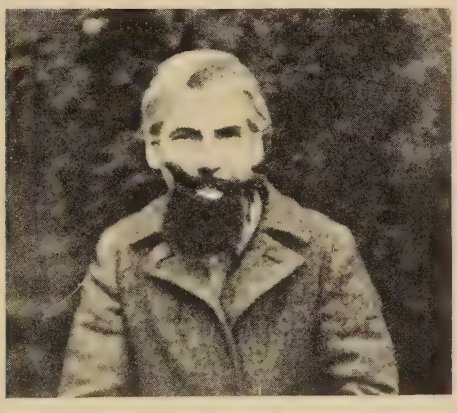

FIG. 2.—The patient with beard.

FIG. 3.—The patient's sister, Polly, aged about 45.

pressure 140/90. There were no abnormal changes in serum or cerebrospinal fluid. The central nervous system was normal except for absent abdominal responses, doubtful right extensor plantar response; all tendon reflexes were brisk, right more than left; both legs were a little spastic. As far as could be ascertained, there was no alteration in joint or muscle sense. Her vision and hearing were normal.

Speech and gnostic functions.—She could not understand lengthy sentences, and gave some incorrect answers. When fresh, at the beginning of the examination, she understood questions relating to herself and revealed that she was aware of her defects. She made certain mistakes, indicating inability to interpret the spoken word, and therefore the naming of objects was imperfect; there was some tendency to perseverate, and she employed paraphasias. There was no true agnosia and no apraxia. Objects could be identified by touch without difficulty.

Reading.—She could understand type and could read parts of sentences, but could not understand what she read beyond a few words. After reading a few sentences she became fatigued and would stop.

Pictures.—She could recognize objects from pictures. A motor car, a fountain pen, a ship, were named accurately. Descriptive pictures, such as a scene and crowds and pictures of actions, were not well understood. The patient could not grasp the whole. The single head of a woman was recognized and was identified as having been seen before when presented immediately afterwards, but the memory was not retained for more than a few moments. Pictures of young men and old were understood, with considerable accuracy. She was able to say, "That is a young man; that is an old man; I do not know that one." She showed great difficulty and much inaccuracy in judging between lines or sticks of different lengths presented to her simultaneously.

Summarizing her speech and gnostic functions, there was a mixed aphasia, sensory and amnesic in form, with impairment of judgment of large symbols and the tendency to pick out details of small portions of presentations instead of the whole. There was no agnosia. Vision and hearing were adequate for these tests.

General mental condition.—She smiled pleasantly when approached, with an evident desire to co-operate. She spoke very slowly, with a slight stammer, which became marked as the conversation proceeded. She soon became tired of the examination and then would speak no more. She admitted and explained that her memory was faulty, and that she had difficulty in finding the words for objects the use of which she understood. She said her memory had been defective for a long time, but had no means of judging how long. She thought that her speech disorder was more recent. She said she used to suffer from severe headaches, but these were now better. She thought this was at the beginning of her illness. She was not sure of her age, but said it would be about 45. She had therefore no idea of the date or the year, or her address, or present whereabouts. When alone she was restless and would wander about as if lost, touching things and evidently searching. When she found herself in front of a mirror or pane of glass, she would immediately stop, smile at her reflection, and refer to it as "Polly." She would then talk with the reflected image and gesticulate. She insisted that Polly was not dead, but that she was "at home."

Diagnosis.—A diagnosis of Alzheimer's presenile degeneration was made.

Subsequent history.—The patient failed gradually. Her aphasia developed so that communication with her became impossible, and her understanding became grossly impaired. As long as she could recognize a mirror she seemed to see Polly as before. She became bedridden and grossly demented, and died 3 years after admission.

Post-mortem.—There was gross wasting of the cortex, and histological evidence of extensive Alzheimer's change in many areas. There were no important focal lesions nor pathological changes in other organs relevant to the case.

Investigations.

Mrs. C—, (62), suffering from Alzheimer's disease, had a serious defect of recent memory, extending back for about 6 years. Her memory for remote events was fairly well preserved, and important early events would be repro-

duced in their proper time sequence. There was a considerable degree of nominal and sensory aphasia, but no apraxia and no agnosia.

When presented with a mirror, the patient immediately identified what she saw as her sister, and this belief could not be shaken. She was unaware that her sister had died, as the death occurred during the period of amnesia.

The question was—what did she really see in the mirror? This was at first sight difficult to investigate, for she was quite consistent in her statements. It was necessary to ascertain first if she could recognize pictures as such, and if so whether they were correctly named or all regarded as likenesses of her sister. Various pictures were presented to her, including a strongly-lined woodcut of a peasant woman, about her age and not unlike her. She replied: "Is this a friend of yours? She is an old woman; I don't know her." It was therefore clear that she did not mistake the pictures, nor link them up with her own particular misinterpretation.

Next it was decided to change her appearance in order to test whether she recognized her sister by a factual resemblance or by a psychotic projection. She was led to the mirror, and at once began to converse with "Polly." While looking at the mirror a large beard was fastened around her chin. She began to laugh and said, "That is me with a beard" (Fig. 2). From this it was clear that by altering her appearance her interpretation of the mirror image was made immediately contemporary and realistic. The mistake was therefore a misinterpretation and not a psychotic projection. When the beard was taken off her expression slowly changed, she looked puzzled for a moment, and then said, as before, "That is Polly."

Next the beard was replaced and she was led about the ward. In a few minutes, on returning to the mirror, she looked hard and said, "That is an old man—is it father?"

From these experiments it could be inferred (1) that she no longer knew what she looked like in a mirror, because any recollection that she had of her face had long since been forgotten; (2) that when she was forced to recognize her face by the distinguishing mark of a beard, she correctly identified it in the mirror, because her appearance had been made immediately contemporary; and (3) that when given sufficient time to forget that the beard had been placed upon her, as she could not recognize what she saw in the mirror as herself, she inferred that she was looking at a bearded man, but, feeling some sort of link with the figure, she guessed that it might be her father, who incidentally in old age wore a beard.

Next she was confronted with a photograph of her sister as she had been at about 45–50, that is, at about the latest date before the patient's memory defect developed, and when she might have had a clear memory of her own appearance. On being presented with the photograph she said, "This is me." As will be seen from photographs (1) and (3) the patient normally parted her hair on the opposite side from her sister, so that in her mirror image the parting would be in the same direction.

It must be inferred, therefore, that although the patient did not realize what she looked like at the time of examination, she retained a sufficiently clear recollection of her appearance at about 45 to enable her to recognize

as herself a photograph of her sister at this age, whom she very much resembled.

Discussion.

This case demonstrates the commonplace fact, which is so often overlooked, that as, unlike inanimate objects, human faces and appearances change with age, it is necessary constantly to refresh the memory of appearance to bring it up to date. Quite normal people feel surprised and even hurt that they have difficulty in recognizing photographs of themselves—regarded as good likenesses—which were taken some years previously. To an even greater extent they have difficulty in identifying their friends. What we believe we know of our external appearance is in fact what we remember from the latest time we have observed it. Further, the latest observation extinguishes previous images, so that we are unable to visualize easily what we looked like at previous periods in our life.

In the recognition of others we depend on accessory senses, such as sound, even smell, and our emotional attitude often predetermines recognition of a subject imperfectly perceived, who perhaps may be misidentified. An attitude of expectancy facilitates identification, so that in normal life mistakes are frequently made, as for example in addressing strangers when waiting on a railway platform. In the recognition of others, perhaps as great a part is played by recollection of patterns of movement as of actual spatial form.

From early days and in primitive people the mirror has been concerned with magic. Women in particular credit the mirror with significance, perhaps even magical powers, and the ability to reveal truth or to flatter. Mirrors in folk-lore are asked not only to tell the owner what she is like, but to make true reflections of matters further afield and even of the future. It is unlucky to break a mirror, and in some legends the shadow or soul of the individual can be trapped and taken away by a magic mirror, as in the legend of Hoffmann.

The mirror in use is not regarded as such. The mirror-gazer looks at what she sees in it and not at the mirror as an object. It is probably for this reason that an agnosia for a mirror is practically impossible without an agnostic failure to recognize at all the person seen within.

As in the cinema, once a sufficient emotional rapport is developed with the image, and this of course is inevitable with a mirror in which an individual perceives herself—the illusion of reality is accepted and the setting is forgotten. The stronger the emotional rapport, the more realistic is the illusion.

In the case of this patient the mirror image was endowed with the strongest emotional qualities for her, so that its reality was accepted immediately it was recognized as her sister, who had acted the role of a parent to her—an attitude not shaken by her marriage, in which the husband played an inferior part. The reality of the mirror situation was accepted as strongly as the screen illusion in a cinema.

A somewhat similar situation is reported by Klein (1928), in which a senile man failed to recognize or identify the image he saw in the mirror, but it was

apparently such a pitiful object that he would make sympathetic gestures to it and then go round behind the mirror to offer it tobacco and sweets.

In the case described perception was impaired, and there was no evidence that she noticed the other objects in the mirror, which served as a background to her reflection. This is in keeping with the results of testing, in which she could pick out details but not grasp complicated wholes.

Recognition was certainly facilitated by a constant expectation that she would soon see her sister, and, as she had forgotten her own appearance, it was easy for her to identify as her sister a woman older than she remembered herself to be, whose movements and facial expressions were probably similar.

Many people feel that reflected images are the true likenesses of themselves and reversed photographs seem less true, so that if the mirror can be disregarded and the image alone perceived, this image would seem to have actual existence, as in the case of this patient, who was incapable of attending to and comprehending the total situation of the mirror, its frame, and the less emotionally interesting objects within, at the same time as the reflected image.

The individual encountered in the mirror must have been either a real person or a reflected image of the patient; the latter was impossible because it did not resemble the younger woman the patient believed herself to be. It was therefore interpreted as someone else, familiar and easily recognized, and the only person with the requisite specifications—visual and emotional—was the dead sister.

It is questionable whether there exists a true agnosia for a mirror apart from an apraxia. A patient might be unable to recognize an actual mirror frame, but, as long as she is able to recognize a reflected image, it must be assumed either that she recognizes the use of the mirror and therefore what it is (having neither mirror agnosia nor apraxia), or else that she fails to recognize herself, which is almost impossible without a gross disturbance of the body scheme and inability to preserve a conception of self, apart from the specific type of situation described here; such a set of conditions is extremely rare.

In this case the operation of several factors must be assumed, namely: severe but localized loss of recent memory; inability to accept the loss of a sister who meant more to the patient than her husband, herself, or anyone else; a restriction in interest and activity consequent on generalized cortical loss, common to all cases of organic dementia, with reduction in ability to make critical evaluation of reality; and a constitutional factor.

The early history showed an abnormal dependence on others and a marked family tendency to psychotic reactions, with, no doubt, in the various cases of schizophrenia amongst near relatives, a tendency to the easy formation of ideas of reference and psychotic projection.

The constitutional factors were most important in producing the special mirror agnosia, which developed primarily from organic brain change, but which would not occur in the absence of multiple factors and a psychotically-disposed constitution. This accounts for the rarity of the picture.

The phenomenon appeared with clarity and was susceptible to analysis, because there were no apractic or agnostic defects, and at first only a relatively small degree of aphasia.

Summary.

In a case of Alzheimer's presenile degeneration, with amnesia for recent events and some aphasia, the reflected mirror image was persistently identified as a sister who had died after the onset of the organic brain process. The mental mechanisms have been discussed, and it has been demonstrated that inability to remember her appearance allowed the misinterpretation to be made. Reasons for the extreme rarity of misinterpretation of mirror image have been suggested.

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CONTRIBUTION TO THE DRESSING DISABILITY AS A FOCAL SIGN AND TO THE IMPERCEPTION PHENOMENA.

By R. E. Hemphill, M.A., M.D., D.P.M., and R. Klein, M.D.,

Bristol Mental Hospital, Fishponds, Bristol.

Inability to dress oneself is a rare symptom in focal brain lesions. We have observed it in two cases, a tumour expanding between the cerebral hemispheres, and a case of head injury in which the mental condition was sufficiently intact to allow a detailed analysis. In discussing the imperception phenomena of the tumour case, we have referred to certain others of relevant interest.

Case 1.—G. R—, aged 42, shop manager, married, no children, gave the following history: About five weeks before admission he noticed a tendency to knock into objects on the left side of his body; he felt he was clumsy, and wondered if it was because of overwork. One evening he was found wandering in the city, unable to decide which way to go. He stated that he had become lost, although the district was absolutely familiar to him. He was brought home and was apparently well enough to return to work next day. He became slow in dressing, and his wife noticed that he put his coat on back to front or got his arms into the wrong holes. He said that he did not know in what position exactly his clothes were or how to put his hands into the arm-holes. Three weeks later a weakness of the left hand developed. It was observed by others He said he had lost feeling and that he had to think sometimes to decide whether the arm was his own. There was a clammy, numb feeling of the left hand, especially when he put it to his face. He thought power was normal, but stated that he had difficulty in picking up objects with the affected hand. About a fortnight before admission he complained one morning of a severe headache and of being sick. He saw double. He remained in bed and could not go to work. Examined in his house, he had great difficulty in moving in bed, he was unable accurately to put on his pyjama coat and there were other organic signs to be described later. He was accordingly admitted to the Mental Hospital. At that time there was no sign of intellectual defect or clouding of consciousness. Previous history was not significant. He was stated to have had a nervous breakdown eight years before, due to anxiety and overwork. He was a right-handed man who had enjoyed good health; his hobby was painting; his intellectual attainments were above average.

On admission: Clinical examination of C.N.S.—Corneal reflex, left less than right; right eye did not reach the maximum position to the right; tongue deviated slightly to the left. Muscular power in left arm was paretic; muscular power at all joints diminished; there was paresis of left leg, less marked than in the arm, more marked in muscles of the large than small joints of the leg. Muscle tone in limbs was not increased; left arm felt heavier when lifted passively. Deep reflexes were brisk and equal; Meyer's reflex present in left. Wartenberg positive on left. Left abdominal reflexes slightly less than right. There were no other pyramidal signs. The gait was hemiparetic, with a tendency to fall to the left. Discrimination of pain and touch were impaired in the left hand only. Localization of touch was less precise in the hand than in other parts of the left arm and left trunk; it was fairly precise in the left leg. The sense of position was absent in all joints of the left arm and diminished in the left leg and toes. Confrontation tests showed left-sided homonymous hemianopia.

He showed great difficulty in naming and pointing to the fingers of the left hand, and made occasional errors with the fingers of his right hand and that of the examiner. When the examiner's hand was placed fingertip to fingertip with the patient's left hand, he was often uncertain as to which was his own and which was the foreign hand. There was no apraxia for handling objects or expressive movements with right hand.

The severe paresis made it impossible to conduct this examination adequately on the left hand or to investigate the dressing disability. His drawing, though still showing signs of skill, was incomplete and dislocated ; sometimes it was quite incomprehensible when he drew lines and curves without formal content. He would frequently pass objects in the left visual field in attempting to point to them or grasp them, but the error was not constantly in one direction. There were no mistakes in estimating absolute and relative distances. The orientation on the map was good. He found great difficulty with even simple jigsaw puzzles ; his performance had no plan, and he took no advantage of the shape of the piece or composition of the picture.

There was no difficulty in recognizing pictures or objects, or interpreting situations depicted. He read well. There were no aphasic disturbances. He could write faultlessly and recognize and name colours. His ability to calculate was intact. When questioned about the paralysed left hand he did not seem to find there was much the matter with it, and when asked to show the left arm he pointed as a rule to the right arm, but made no such mistakes when concerned with other parts of the body.

Progress.—The history and symptomatology pointed to a tumour of the right parietal region. Accordingly the patient was transferred to a neuro-surgical unit. He became rapidly worse, and five days later there was an almost complete paralysis of the left limbs and atrophy of the interossei and thenar muscles of the left hand. The eyes deviated to the left. There was definite bilateral papill-oedema. The finger agnosia and attitude towards the left arm remained the same. The patient died two days later.

Post-mortem findings.—On cutting the dura there was a tumour loose between the two hemispheres. It was the size of a small apple, with a number of nodules of greyish colour and hard consistency. On sectioning, it appeared that the loose tumour represented an extra-cerebral outgrowth connected with an intra-cerebral portion by a thin connecting band which had been torn at post-mortem. The extra-cerebral portion was in contact with the right most posterior parts of the cingulum and precuneus just above the splenium in front of the parieto-occipital fissure.

The extension and damage to the brain substance of the intra-cerebral part were studied in cross sections. This showed occipitally frontalwards that the right posterior horn was completely obliterated by a soft mass of tumour tissue infiltrating the occipital lobe, mainly towards the medial surface and here extending close to the grey matter of the cortex (Fig. 1). In the next two sections the tumour, infiltrating towards the convexity, destroyed the white matter of the angular gyrus and the posterior part of the supramarginal gyrus, but left the white matter close to the cortex macroscopically intact. The tumour infiltrated basically the splenium of the corpus callosum, and a thin band connected the extra- and intra-cerebral parts of the tumour.

The thalamus posteriorly was completely isolated from the cortex ; the projection fibres were destroyed. Its ventricular surface was flattened and compressed, the vertical diameter smaller, the horizontal larger, than on the left side. There was a wide communication between the temporal horn and the posterior part of the lateral ventricle. The basal convolutions on the right appeared distorted upwards to the level of the thalamus, the cornua ammonis being higher. Thus the vertical diameter of the right hemisphere appeared in these sections to be much smaller than the left (Fig. 2).

On section the tumour was brittle, with wide areas of softening. Stained with haematoxylin-eosin, it was cellular with little stroma and vascularization. It consisted of cells of epithelial type forming pseudo-rosettes, with areas of less differentiated cells of varying shapes and deeply stained nuclei. Faintly-stained nuclei packed close together were seen in the softened areas. The muci-carmine stain was negative. The tumour belonged to the malignant ependymoma group (Kernohan and Fletcher-Kernohan, 1935).

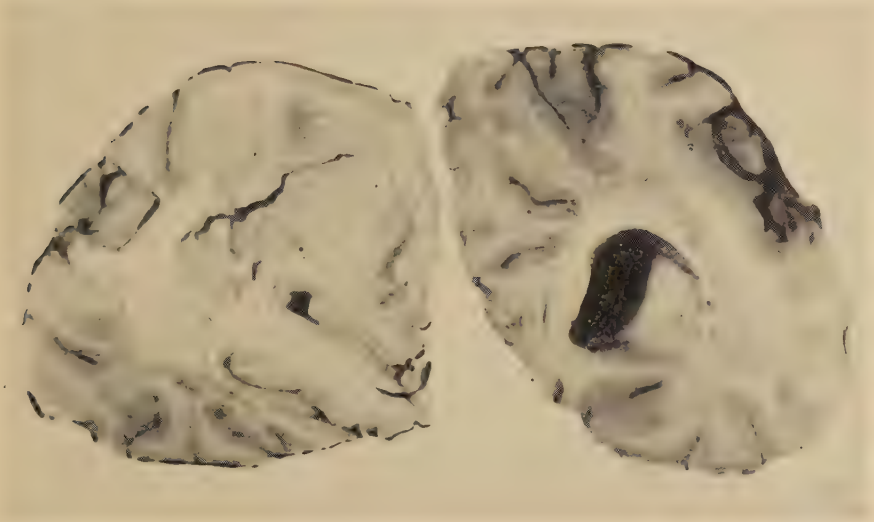

FIG. 1.—Cross-sections through each hemisphere, showing the intra-cerebral portion of the tumour obliterating the right posterior horn and infiltrating towards the occipital cortex.

FIG. 2.—Posterior portions of the right thalamus are severed and the right corpus callosum destroyed. Indentations on the medial surface of the right hemisphere indicate the position of the extra-cerebral portion of the tumour.

Tumours extending from the posterior horn through the corpus callosum into the interhemispheric space are rare. The extra-cerebral portion was not likely to produce clinical symptoms in its position. It must have grown for a considerable time before the intra-cerebral portion began to infiltrate, thus accounting for the late onset of symptoms and rapid final course.

There were two phases in the clinical course, separated by about three weeks. In the first there were local symptoms : left-sided hemianopia, spatial disorientation and dressing disability, but without signs of mental or other physical illness, and no evidence of increased intracranial pressure.

In the second phase pressure symptoms appeared, with slow cerebration, loss of interest, decreased attention, poor memory and retention and fresh focal symptoms. There were left-sided hemiparesis and hemihypaesthesia, maximum in the left arm, loss of sense of position in the left arm, imperception of the defect of the left side, with tendency to neglect the left arm, inability to distinguish the left hand from a foreign hand, and inability to draw ; with finally atrophy of the small muscles of the left hand and deviation of the eyes to the left.

There are few reports on dressing disability in focal lesions. Marie, Bouttier and Bailey (1922), described planotopokinesis, with difficulties in dressing, disturbance in fine finger movements, disorientation on the map, acalculia, and spatial disturbance of writing ; there were some disturbances of body space (Head test). There was no apraxia, no visual disturbance, no disorientation in space.

There was a similar symptomatology in a second case. Marie *et al.* (1922) regarded the basic disorder as a defect of spatial representation.

Kroll and Stolburn (1933) described dressing disability in a case with left-sided hemiparesis and hemihypaesthesia, defective attention in the left visual field without hemianopia, object apraxia, disturbance of writing and drawing, space disorientation and acalculia. These authors considered apractic disorder as the common factor.

Klein (1933) has described a case with dressing disability in a complex setting of aphasia and apraxia.

A case described by Alajouanine, Thurel and Ombredane (1934) presented difficulties in dressing, a left-sided homonymous hemianopia and disorientation in space and time. This patient was not aware of the existence of his left arm, although movements were intact, and showed astereognosis and apraxia in the left arm only, agraphia, almost complete alexia and inability to draw. These authors postulate a special type of somatagnosia of the left arm, combined with spatial disturbance—the planotopokinesis of Marie.

Lhermitte (1937) reported two cases of inability to dress, one accompanied by apractic-constructive disorders, the other by agraphia and autotopagnosia for the left side of the body and apractic disturbance in expressive movements. He assumed interruption of connections joining kinaesthetic and visual with psychomotor functions, without disturbance of spatial conception.

Brain (1941) described two cases, and referred to two cases reported by Jackson (1876) and Wendenburg (1909). In Jackson's case there was a right-sided temporo-parietal tumour, with left hemiplegia and imperception,

and spatial disorientation with good topographic memory. In Wendenburg's case there was a tumour in the right occipital lobe ; there were visual object agnosia, spatial disorientation, and difficulty in dressing.

In one of Brain's cases it was reported that, following an injury of the left superior parietal lobe, there were aphasic disturbances, acalculia, right-left disorientation, feeling of strangeness of the right half of the body and visual disorientation in the right homonymous half-field. In the second case there was a tumour of the right parieto-occipital region, producing dressing disability, with left-sided homonymous hemianopia, dysaesthesia and left allaesthesia, loss of position on left side, spatial disorientation, with neglect of left half of the external space.

Brain concludes that inability to dress may be a special apractic disorder, closely related to disorders of one half of the body ; a lesion in either hemisphere disorganizing the body-scheme might produce it.

Our second case is similar to that of Brain :

Case 2.—A. B—, aged 32, incurred head injury and was admitted to hospital after several hours of unconsciousness. Apparently he was completely blind, paralysed on left side, and had difficulty in expressing himself. He regained sight in a fortnight ; had difficulty in reading for several months more ; his speech improved at about the same time, and there was some improvement in paralysis.

When examined by us two years after the injury there was a left-sided paresis and hemihypaesthesia, most marked in the hand ; loss of position sense in left fingers and hand, diminution in other joints of the left arm, and slight disturbance in the small joints of the left leg. There was astereognosis in the left hand. There were left-sided homonymous hemianopia and marked constriction of the right field.

The patient reported difficulty in dressing and in spatial orientation and a strange feeling on his left. He stated that for several months after the accident he would lose himself in familiar places, and did not know which way to go on routes he formerly knew well. There was no difficulty in recognizing buildings and landmarks, and he was always able to orientate himself in hospital and in his own house.

Two years after the accident, when we examined him, this disability had improved and he rarely had to think which way to go. He noticed on waking a feeling that his left arm did not belong to him, and occasionally would forget to fit his shirt over his left arm. There was always a feeling of unfamiliarity in the left arm.

Dressing disability : He had great difficulty in dressing himself. He could not do it at all without first laying out shirt, coat, and trousers. This preparatory act was a serious problem. He would turn his clothes round and could not make up his mind which was the front and back, and when he did put on a garment he often put it on the wrong way. This improved some time after the accident, but some disability remained ; he had difficulty in deciding which was the right and which the left shoe, and often put his shoes on the wrong feet.

He had lost much of his skill as an engineer. He found it difficult to put together parts which had been taken to pieces, and simple automatic manipulations with instruments would often cause difficulty.

There was no disorder of speech ; no alexia or agraphia ; visual gnostic functions for objects, pictures of objects, and situations in pictures were intact. His history did not indicate that visual apperception had ever been impaired. Colour naming and sorting was done quickly and accurately. He estimated relative and absolute distances well. There were no errors in pointing to various areas of the body, and right-left orientation of the body was unimpaired. There was no apraxia for ordinary objects or in expressive movements. Calculations were made slowly but accurately. Free-hand drawing and copying of geometric figures (Abelson) were defective. Drawing a hand, he put the little finger at the same distance

from the other fingers as the thumb ; drawing a face he could not put the different parts in correct relation to the others. Copying was laborious and inaccurate. He was slow in doing jigsaw puzzles, but could do even complicated puzzles by considering every step carefully. Orientation on the map was difficult ; at first he did not know where to look for a place, and then became confused between east and west.

Summary of the case.—Two years after a traumatic lesion involving the right parieto-occipital region and possibly left visual area there were left-sided hemiparesis and hemihypaesthesia, left-sided hemianopia, a feeling of strangeness and occasional ignorance of left arm. There were constructive disorders, difficulty in spatial orientation, and marked difficulty in dressing. It appeared that the fundamental disturbance was of visual-spatial character. He failed to differentiate sufficiently between the geometric elements in objects and was therefore unable to relate objects with regard to their shape ; whenever the situation required adjustment of two objects with details of their shape, difficulty arose. This explains the constructive disorder and difficulty in dressing. The defect in visualizing objects, with the same defect in visual imagery, accounts for the disturbance in space orientation and free drawing. This disorder is similar to geometric agnosia (Pötzl), but not confined in these cases only to abstract figures.

All the reported cases show that there is much variability in the symptoms that accompany disability of dressing, but prominent are apraxia and visual agnosia, especially of spatial character, and disturbance of body scheme. In the complex act of dressing, garments that belong to outside space have to be incorporated in the body scheme by a kinetic formula. Adequate apperception is necessary. Relations between body and outside space have to be so established that body shape can be related to the shape of the garment, and appropriate movements have to be carried out to transfer from one space to the other.

In both our cases there was a spatial-agnostic defect. In the first case there were spatial disorientation and dressing difficulty ; in the second, disorientation, constructive disorder and confusion in dressing, due to defective recognition of geometric details and the spatial signs of an object. In both cases the right non-dominant hemisphere was involved. The predominance of lesions in the non-dominant occipital lobe in spatial disorientation is thus related to disability in dressing when there is a visual-spatial defect.

In the second stage in the development of the first case the patient treated the paralytic side in two different ways ; he overlooked the left side and reacted as if it were absent, but was unable to realize its functional loss. Two types of imperception phenomena can be distinguished : unawareness of the defect (anosognosia, Babinski), and neglect of or amnesia for the defective member. In the first, the defective member is fixed in its pre-morbid condition in the body scheme, in the other excluded from it. These two attitudes would appear to exclude each other. In our case the left half of the body seemed to be represented in the body scheme in both ways.

Case 3.—The same paradoxical attitude was found in the following case : A 77-year-old senile, with severe memory loss and some tendency to confabulate, showed, after an apoplectiform seizure, deviation of eyes and head to the right with loss of conjugate eye movements to the left, absent lid-blinking reflex on the left, left-sided hemiplegia and hemianaesthesia and loss of position-sense of the left joints. When asked to point to parts of the body, she never passed her intact right hand above the midline to the left, but made no mistakes when pointing to parts of the right half of the body. She was unaware that her left side was

paralysed. When the left arm was brought into her visual field and she was asked to move, she made movements with her right hand and would not realize that she could not do so with her left. She also related that she took walks when actually she was lying helplessly in bed. A few days later the deviation of eyes and the paresis of conjugate eye movements disappeared; she was able to make slight movements of her left shoulder and elbow and ample movements of ankle and toes. Position-sense in arm was still absent. There was complete anaesthesia at first; later she localized on the chest stimuli applied to the arm. Sensation in other parts of the body was normal. She could point to all parts of the body on the left side, and only occasionally showed a tendency to point to the right instead of the left. She was, however, as before, unaware that she was unable to move the paralysed limbs.

After a fortnight the patient died. The brain showed a moderate atrophy of both frontal poles, the right hemisphere was somewhat smaller than the left, and there was a softened area on the surface of the convexity extending from the posterior end of the right inferior frontal convolution to the angular gyrus. In frontal sections damage was most severe in the transition area of the inferior frontal lobe and precentral gyrus, where it extended deeply into the white matter close to the striatum. In posterior central, supra-marginal and angular gyri the gross damage was confined to the cortex and the white matter close to it; the thalamus and its peduncles appeared intact.

In this case the deviation of head and eyes to the side opposite to the hemiplegia seemed to have been a factor in the imperception phenomena: with disappearance of the deviation, the patient became again aware of the left half of the body previously neglected, although she still could not realize it was paralysed. Turning away from the affected side, mentioned in several cases in the literature (Kramer, 1914; Pötzl, 1926; Hagen, 1937; Brain, 1941), introduces a visual-spatial element into the imperception problem. Attention has been drawn by Brain (1941) to such visual-spatial relations. This author reports three cases in which unawareness of one half of the body was associated with neglect of the corresponding half of the external space, and he points out that body image and outside space are closely connected anatomically as well as functionally. Anatomically, the lesion which causes both these disorders is situated between the visual and the postcentral area; functionally, an object of the external space has no meaning except in relation to the body scheme.

These relations are, however, not one-sided. Body parts (and this applies especially for the limbs) are in two ways related to the external space: though body-bound, they are part of the outside space, and as tools of the body they are functionally oriented towards this space. When we move the arm from the limp position into extension forward, we have changed the position of the arm towards external space as well as towards body. Both these relations are contained in the normal image of the body, and have to be continuously registered under control of visual and positional sense.

The third case here reported suggests that such spatial factors were involved: the interrupted contact, the virtual abolition of the left half of space, which includes the left half of the body, caused by a combination of deviation and hemianopia, were the ultimate cause of the neglect of this half; the complete loss of sensory perceptions from the left half of the body deprived our patient of all perceptive sources from which to be aware of this side.

This case shows that the unawareness of the hemiplegia was conditioned by factors different from those which caused the neglect phenomenon, for

when the patient had become aware of her left side she was still unaware of the hemiplegia. What special conditions might underly the imperception of the defect is indicated by the following case :

Case 4.—A woman, aged 35, with bilateral optic atrophy for 15 years, was blind for 14 years. Later the lower limbs were immobilized by advanced ataxia. She was mentally intact until just before her admission to hospital with taboparesis, and was fully aware of her condition.

Neurologically there was loss of deep reflexes, impairment of positional sense in the lower limbs, and severe ataxia, which made standing without help impossible. Mentally there was intellectual deterioration of Korsakoff type.

The patient would admit neither blindness nor inability to walk ; she maintained she could see, and would describe persons or objects which she believed confronted her. She showed the same attitude towards her motor defects ; she reported walks she took, and denied consistently that there was anything wrong with her legs.

In this, as in the case described by Stengel and Steele (1946), intellectual defect superimposed upon a chronic functional loss caused the phenomenon of unawareness.

In these cases certain points are significant. With the same anatomical lesion, unawareness of defect as well as elimination of the defective side may be present (Cases 1 and 3). One of these phenomena may disappear, the other persist, after partial restitution of function (Case 3). Case 4 shows that unawareness of a longstanding defect may appear only when intellectual deterioration is advanced. Case 3 demonstrates the relative independence of this phenomenon from the physiological condition.

In all cases loss of perceptive functions is the most important factor in the neglect phenomenon. The extent and intensity of this functional loss will decide whether a sense of strangeness or occasional forgetting of the affected side appears, as in our Case 2, where the neurological defect is moderate ; some neglect of the affected side, as in our Case 1, where the functional loss is considerable ; or total neglect, as in Case 3, where the perceptive loss is complete. Strangeness, occasional forgetting and neglect are variations in degree of the same disorder. They represent errors in ability to construct an image of particular parts of the body by perceptive means ; alteration and reduction of the respective perceptions reduce the capacity to evoke an appropriate picture and feeling of reality for parts of the body.

On the other hand, unawareness is not due to faulty perceptions, and the construction of the body image is not involved. It is not the particular parts of the body, but their functions that are experienced abnormally. The functions concerned, moreover, can be of quite different order ; the phenomenon can be seen in peripheral or cortical blindness, in aphasia, in hemiplegia. Different functions (visual and locomotor) can be involved simultaneously, indicating a more general disturbance. Case-reports in the literature (Redlich and Bonvicini, 1914–5 ; R. Klein, 1924 ; Pötzl, 1923 ; Hagen, 1937 ; Klein and Mallie, 1945 ; Redlich and Dorsey, 1945 ; Stengel and Steele, 1946 ; *et al.*) show that a general impairment of cortical functions is the rule in anosognosia.

Lesions of the parieto-thalamic region in the right non-dominant hemisphere are held responsible for imperception (Pötzl, 1923). It is thought that

the right parietal region integrates sensory perceptions (Pötzl, 1923 ; Nielson, 1938–40), and the imperception phenomena appear when sensory stimuli are prevented from reaching this part of the brain. All the cases cited and all ours are in agreement for the neglect phenomenon. As corresponding lesions of the left dominant hemisphere do not produce the same disability, it would seem that such integrating functions exist for the left half of the body only and not for the right, which is certainly difficult to understand.

There are two possible reasons for the rarity of imperception phenomena in left-sided lesions : the particular site of the lesion which generally causes these phenomena, and its transitory character. As lesions of the left thalamo-parietal region are usually complicated by aphasia and apraxia, imperception phenomena will be difficult to demonstrate, as this requires understanding and co-operation. The transitory character becomes important under these conditions, for the phenomena may have disappeared at a period when the complicating symptoms have so far improved as to permit proper investigation. Close observation may sometimes indicate imperception phenomena even in the initial stages of lesions in the left hemisphere, as the following case shows :

Case 5.—A patient, aged 56, who suffered from general paralysis of the insane, had an apoplectiform seizure producing right-sided hemiplegia, hemi-hypaesthesia, and total aphasia. His speech became almost inarticulate, and there was little understanding of the spoken word. He had a tendency to clasp the right paralysed hand in front of him. When the right hand was passively abducted and he was asked to show his right hand, he made unsuccessful grasping movements in front of him as if the hand were still there. He never turned eyes or head to the right in order to bring the right hand into his visual field. If, while his own hand was passively held to the right, the examiner's hand was put before him, he clasped it in the same way as he did his own right hand, apparently in the belief that it was his.

He died six weeks after the seizure. The brain showed moderate atrophy of both frontal lobes. A softening destroyed almost completely the 1st and 2nd left temporal convolutions in their entire length, extending backwards into the supra-marginal and angular gyri and the bordering occipital convolutions. On cross section a small area of softening was seen in the head of the caudate nucleus, and a strip-like softening in the white matter of the posterior central gyrus which extended towards the internal capsule. There was otherwise no damage to the deeper layers of the white matter ; the thalamus and its cortical peduncles appeared to be macroscopically intact.

There was therefore in this case of a left-sided lesion in a right-handed person an abnormal attitude towards the paralysed right arm with a neglect of the limb. There is therefore evidence that the theory that lesions of the right inferior hemisphere are specific for imperception phenomena is not entirely sound.

Nielson, in elaborating Pötzl's supposition, assumed that there are different anatomical localizations for the anosognosia and the neglect phenomenon. He is of the opinion that in cases of neglect of one half of the body the essential lesion is in the parieto-thalamic peduncle ; in anosognosia either the thalamus is directly affected or it is separated from the frontal, parietal and temporal lobes. In our tumour case the parieto-thalamic peduncle was destroyed, while all other thalamo-cortical fibres were intact. This agrees with Nielson's assumption concerning the neglect phenomenon, but not as to the anosognosia

which was simultaneously present. In our third case, in which both imperception phenomena were present, there was widespread damage of cortical areas, with little involvement of subcortical layers and macroscopically intact thalamo-cerebral peduncles; this does not agree with what Nielson expects, either in anosognosia or in neglect of one half of the body. There is no support for Nielson's theory in the anatomical findings of the last case.

Our own and published observations suggest the following conclusions: Unawareness of a defect can occur whenever deficiency or loss of function appears. It is due to a general impairment of cortical functions, which can be caused by a variety of generalized processes. The unawareness of a hemiplegia is no exception; there is no evidence that the focal lesion by itself leads to this phenomenon.

The phenomena of strangeness and neglect of one half or parts of the body are pathophysiologically conditioned, and due to loss of perceptions which normally are used for realization of these particular parts and for construction of an image of them. It may be that this integration takes place in the parieto-occipital region. As in the parieto-thalamic area the fibres conducting elementary perceptions of one half of the body are concentrated, lesions in this region are bound to be important in disorders of the body scheme. The clinical experience that neglect and kindred phenomena are mainly seen in lesions of this area is therefore no proof of specificity of the parieto-thalamic region, nor is there enough evidence that the right non-dominant hemisphere has a special significance.

In anosognosia, presumably due to a generalized process with lowering of mental capacities, the patients are unprepared to face the defect, and there is a tendency towards fixation of the pre-morbid body image. In the neglect phenomena, due to a circumscribed functional loss with preservation of functions at a higher level, the tendency is to eliminate the useless body parts from the body scheme.

In Case 1, at the period when the imperception phenomena were found, difficulties in drawing and finger-agnosia were present. The definite spatial disturbances in the drawings probably related to the visual spatial disorder prominent in the first stage of the illness. The finger-agnosia was mainly confined to the left hand; but, because of the paresis, possible agraphic or dyspractic disturbances could not be assessed. Finger-apraxia of the left hand resembles and is functionally related to the isolated dyspraxia of the left hand which, according to Liepmann, is due to a lesion of the corpus callosum. This widely-held opinion has recently been disputed, for it has been shown that destruction of the corpus callosum is not as a rule followed by dyspraxia. The observations of Akelaitis *et al.* (1941) offer an explanation for the contradiction. They sectioned the corpus callosum in 18 cases of epilepsy, and found that dyspraxia of the left hand occurred whenever the right subordinate hemisphere had been damaged before or during this operation. In our case there were lesions of the right hemisphere and of the corpus callosum; combined lesions may thus have been the cause of the left finger-agnosia.

Another possible explanation for finger-agnosia in a lesion of the right non-dominant hemisphere would be a shift of dominance, assuming that the

right inferior hemisphere remained inferior with regard to spatial orientation, but dominant for finger-agnosia.

In a broader physiological sense, the finger-agnosia is part of a de-differentiation of the hand, which can be found (Klein, 1932–3) in parietal lesions at all functional levels. Expressing this, there arose in Case 1 a paralysis, a sensory loss of the hand, inability to distinguish the hand from a foreign hand, a tendency to eliminate it from the body scheme, and finally, atrophy of the small hand muscles.

Summary.

A case has been described in which a malignant ependymoma of the right posterior horn infiltrated through the splenium, severed the posterior portion of the thalamus, and formed an extra-cerebral outgrowth in the interhemispheric space. Clinically, two stages could be distinguished, the first showing a left-sided homonymous hemianopia, spatial disorientation, and dressing disabilities, the second, a left-sided hemiplegia and hemianaesthesia, finger-agnosia and imperception phenomena.

Dressing disability and spatial disorientation were more fully analysed in a patient in which they persisted, with left-sided symptoms and tendency to neglect the left arm, after a head injury. They were related to a spatial disorder of geometric agnostic type. In discussing the imperception phenomena, the case of a senile is described in which these phenomena appeared after a seizure, together with a left-sided hemiplegia, hemianaesthesia, homonymous hemianopia, and deviation of eyes and head to the opposite side. The neglect phenomenon disappeared, whilst the anosognosia remained unchanged, after considerable neurological improvement. Autopsy showed an extensive cortical softening with little damage to the white matter; the thalamus and its peduncles appeared macroscopically intact.

In a case of tabo-paresis with severe locomotor ataxia and blindness due to optic atrophy, imperception of these defects appeared after the mental deterioration had set in.

Finally, a case of general paresis is described, in which a vascular lesion of the left hemisphere caused a right-sided hemiplegia and hemihypaesthesia, hemianopia, and a pathological neglect of the right arm.

It has been concluded that the neglect phenomena are due to perceptive loss in the half or part of the body involved, leading to defective realization and inability to construct an image of these particular parts. There is insufficient evidence to suggest that the right non-dominant hemisphere is of greater importance for the body scheme and its defects than the dominant left hemisphere. The parieto-thalamic lesion is not specific, though for physiological reasons it frequently produces this phenomenon. In anosognosia of one half of the body, construction of the body scheme is not at fault, but the main factor is a general impairment of cortical function. There is no evidence that the focal lesion which causes the unilateral neurological signs is responsible for the anosognosia.

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THE COMMUNITY AND THE AGGRESSIVE CHILD.*

By J. D. W. Pearce, M.A., M.D., F.R.C.P.E., D.P.M.,

Co-Director, Institute for the Scientific Treatment of Delinquency; Hon. Psychiatrist, Queen Elizabeth Hospital for Children; Hon. Physician, Tavistock Clinic.

A subject such as this is much too large to deal with at all fully in a short paper. As it is designed as a preparatory review of this topic as it applies to Great Britain, the subject being dealt with at the International Congress of Mental Health by delegates from overseas, I am placing the emphasis on the community rather than on the aggressive child. It is necessary, however, to consider what the aggressive child does to the community and why, in addition to discussing what the community does to the aggressive child, and the reason for this.

A. F. Shand (1), in his *Foundations of Character*, says that when the activity of an instinct is most sudden and unopposed, the emotion, if it be brought into activity at all, will be of less intensity and definiteness. In the activity of the instinct of aggression it is well to remember that the emotional experience or tension may be quite slight. One's experience of large numbers of aggressive children is that this applies very much to most of them. Their aggressive conduct occurs without there being any strong emotional experience accompanying it. Drever (2) takes the view that the instinct-emotion is not an invariable accompaniment of instinctive activity, but is due mainly to arrest of the impulse, to the denying of immediate satisfaction to the interest. Such denying of immediate satisfaction with its resultant development of instinct-emotion is an impetus to more aggressive conduct. McDougall (3) says very truly that with all specific instinct tendencies the constant and characteristic quality is an emotional experience of a quite specific quality. The more common specific instinct tendencies, which in point of fact spring from the primary instinct of aggression and are commonly notable in the aggressive child, are anger, self-assertion, and acquisitiveness.

The question of the strengths of instinctive drives in different individuals is one about which little seems to be known. Is it analogous with I.Q. in that different individuals are differently endowed, quantitatively and qualitatively? It would seem to be so, but the way in which cerebral destruction, as in encephalitis lethargica, can release an overwhelming force of aggression points to the contrary.

The aggressive instinct subserves many socially worthy purposes. In clinical work as a psychiatrist one tends to dwell mainly on the asocial and antisocial manifestations of this instinct. Also in practice the emphasis is on the bad effects of frustration, but frustration may be a starting-point for

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many valuable aggressive reactions, and such cases naturally rarely come before the psychiatrist. It is necessary to state clearly at this point that aggressive attitudes and conduct do not by any means all spring from frustration ; in fact, only a minority do so. Much aggression is actively encouraged by the precept and practice of individual members and whole sections of the community, these being communally aggressive either in a socially good or a socially bad direction. Group membership may conduce to much aggressive activity. This may be good, as, for example, in membership of a rugby team ; or it may be bad if one is a member of a gang of thieves. But for the recent national communal aggression of 1939–1945 it is doubtful if it would be possible for this paper to have been compiled.

Such communal forces play no small part in the development of the child's superego. It is perhaps a mistake to regard a superego which approves of antisocial aggression as therefore undeveloped. It should be regarded as normally developed, though socially in a scarcely praiseworthy direction. It is not a matter of under-development but of wrong development. Examples of the latter are the many children who have incorporated the delinquent standards of their parents.

Healy and Bronner (4) say that ethical concepts which have no personification have little force in the lives of young people. This applies outside the family as well as within it. The community provides many contrary personifications, good correcting bad, and bad undermining good. The mechanisms of projection and identification are applied not only in relation to individuals outside the family, but also in relation to groups which the child finds emotionally satisfying, and these play their part in the development of his character. The most outstanding present-day instance of this is seen in German children.

A child has three main methods of expressing his aggression upon the community. The first is by truancy and vagrancy. Truancy is essentially an aggressive act in that it is a positive rejection of the demands and requirements of the community. Really serious frustration is the usual precipitating condition. Teachers as figures of authority may be the irritant ; or there are difficulties with other children ; or the school work is either too difficult or, being too easy, boring, etc. It is well to remember that many a child fails to respond aggressively to such a difficulty, and instead of truanting he suffers in silence. This quiet submission to difficulties may be thought to be a bad thing. The very fact of truancy may lead the community to perceive its mistake, and by rectifying this the child's problems may be remedied. Surely it would be better if such primary miseries did not occur at all. There is need for much more research into the interpersonal relationships and tensions within the world of school-life. Equally important is the need for application of personnel selection and job analysis techniques.

Children who run away from home are usually escaping from situations which they have found to be intolerable. This is an aggressive act, as aggression has been mobilized and thereby a solution attempted. What is the reaction of the community? So often it insists that the child return to the intolerable situation, to which he then either submits, whereupon the community feels " it has won " ; or he runs away again, whereupon the community feels " it

has failed." It is not unknown that a Juvenile Bench should resort to the judicial birching of such children.

Boarding schools provide their problems also. In one instance a boy ran away many times, chiefly out of dislike for the headmaster. After being returned to the school for perhaps the tenth time he was thrashed rather severely, and not unnaturally, ran away once more. Though it was advised by the psychiatrist, who happened to see him and examine the rather deep bruising, that he should not be returned to that school, the unfortunate boy was returned a day or two later. The psychiatrist's suggestion in this case was that if this policy were to be pursued, the next step, to be consistent, should be in some way to render him incapable of running away, by adopting the methods in use a good many centuries ago. That the community can be so unresponsive to the sufferings of children must be a matter of serious concern to those who have these matters at heart.

Many boys and girls live in places such as orphanages, which do not seem to produce overtly aggressive children. This is admittedly an overstatement, but one does tend to recognize their curiously submissive, uninspiring products. Perhaps society has failed to a greater degree in its responsibility when such is the result than had it produced rather irksomely aggressive children. Therapeutically it is less difficult to help a child to bring aggressive tendencies under control than it is to release aggression which has been very firmly suppressed. The question which one has to ask is what has the community done about all this.

The second main antisocial technique employed by the aggressive child is stealing. Nearly all stealing habits start in childhood. It has been said that if there were no receivers there would be no thieves : it would be nearer the truth to say that if children did not learn to thieve there would be few adult thieves. Bowlby (5) in his *Forty-four Juvenile Thieves* has focused attention on the affectionless child. His figures are, however, misleading as his cases were all highly selected in that they had been referred to a psychiatric clinic. With the common run of juvenile thief the percentage of such affectionless children is very small. This is not to suggest that they are an unimportant group, but they comprise only a small fraction of the total problem. Most juvenile thieves steal at first either by following the example of others, or as one outcome of a psychopathic or near-psychopathic state. Mental deficiency, organic disease, reaction character-trait formation, psychoneurosis and psychosis account for nearly all the others, either directly or indirectly. The great bulk of juvenile stealing is done in the company of others. In many cases the gangs are well organized, various roles are allotted and recognized leaders are in command. Adults are very often behind them, at least as receivers. In many such cases the elements of frustration for which we seek as perhaps underlying such conduct are so slight that they have but minor, if any importance.

A large toll of injury is sustained by the community at large, but the child's own community, i.e. his confederates, approve of him. Perhaps it should be said that the writer has examined a great number of juvenile thieves, admittedly some more thoroughly than others, and their conduct is usually linked

neither with anxiety nor with self-criticism. Their one source of reproach is that they have been caught.

One may ask what the community at large does to these children. Too often it is vindictive or, at the least, unintelligent, though in many districts such as London there are imaginative and responsible sections of the community. Outstanding examples of this in London are the Juvenile Court Magistrates. Surely there need not be so many children behaving in such ways.

The aggressive child's third technique is by directly aggressive conduct, which extends from bullying, damage to property, the spreading of defamatory rumours right up to murder. Usually there are no secondary mental mechanisms involved; the conduct represents a direct outpouring of the aggressive instinct, which in no way puts the superego out of countenance. Again the question is what does the community do. An extreme example of its response was in the case of a boy 13 years old, who was charged with rape and murder, but found not guilty as the law, i.e. the community, said that, as he was not yet 14 years old, he was therefore physically incapable of perpetrating the first offence, and mentally incapable of committing the second. His response to these findings was just what one might expect.

In a short paper such as this no exhaustive analysis of the community and its influences is attempted. A superficial description of major factors serves best as a basis for later discussion and thought.

The most important elements in the community are school-life, the neighbourhood in which the child lives, civic and national attitudes and religion.

Many situations infused with aggression occur among school children, and much bullying undoubtedly goes unchecked. Many school teachers appear to be far less interested in the children under their care as children than in the task of putting them through the school curriculum. The spotlight is on academic learning. This is a subject worthy of some hard thinking.

Outside school and the home there is the neighbourhood. Some districts are good and others bad, materially, morally or both. There are streets where everyone is a thief. There are districts into which the police do not go in units of less than two. The neighbourhood may be rich in temptation, and may at the same time provide much frustration. Society so often fails to encourage the freedom of its members, and in so many ways older persons seem unwilling to allow a child to participate in their corporate life that there is little cause for wonder if the child feels thwarted and his aggression is aroused. Add to this all the other positive opportunities of and incitement to aggressive and antisocial conduct.

Civic and national attitudes with all their political strife, class warfare, tensions and strikes, so faithfully reflected in the press, by the radio and on the screen, are in many ways pernicious in their influence. The wealth of detailed factors which are active in this way need not be discussed now. It is important to remember that it is just these communal attitudes which are so liable to undergo constant changes. In a nation at war the very qualities which are condemned in times of peace are set up for emulation. It may be thought that true religious feelings and perhaps even the experience of any formal religious teaching are useful in superego development. There may be

those who consider this to be a poor form of control, but none the less it is surely better than none. Whatever one's views, there is no escaping the fact that religion has declined and is continuing rapidly to decline as a force in the individual and communal life of this country. Coincidentally, there is a great increase in the overtly aggressive behaviour of individuals and of communities. This situation would repay exploration. Last year the entire membership of the group for Advancement of Psychiatry present at a meeting unanimously approved the statement on the relationship between psychiatry and religion, which is as follows :

" For centuries religion and medicine have been closely related. Psychiatry as a branch of medicine has been so closely related to religion that at times the two were almost inseparable. As science developed, however, medicine and religion assumed distinctive roles in society, but they continue to share the common aim of human betterment. This also holds true for that method of psychiatry known as psychoanalysis. We, as members of the Group for the Advancement of Psychiatry, believe in the dignity and the integrity of the individual. We believe that a major goal of treatment is the progressive attainment of social responsibility. We recognize as of crucial significance the influence of the home upon the individual and the importance of ethical training in the home. We also recognize the important role religion can play in bringing about an improved emotional and moral state.

" The methods of psychiatry aim to help patients achieve health in their emotional lives so that they may live in harmony with society and with its standards. We believe that there is no conflict between psychiatry and religion. In the practice of his profession, the competent psychiatrist will therefore always be guided by this belief."

The late Dr. Ira S. Wile (6) considered maladjustment in the happiness and behaviour of children to have grown out of customs, laws, regulations and ordinances, rather than wholly out of ignorance, misunderstanding and inherent frailties. In his view the main general sociological causes fall under the three headings of social sanction, social tolerance and social indifference. It is on these three main conditions that attention should be focused. They constitute a sickness of society. Society does sanction so many undesirable things. Many others which it may not go so far as to sanction it regards with tolerance : and to those which it neither sanctions nor really tolerates it is so often largely indifferent. This is the main social disease which a study of the community and the aggressive child illuminates. The field for research is vast. An excellent pilot-run would be a comparative study of the aggressive child in different communities, such as Italy, Spain, Switzerland, Sweden, the United States of America and Great Britain. The Briton's horror of what he regards as the cruelty of the Spaniard to animals is no greater than the Spaniard's horror of what he regards as the Briton's cruelty to his children. A second very fruitful field for research would be a comparative study of the influence of the impact of religion on communal attitudes, and the part religion plays in the communal consciences of a variety of nations.

In thinking about the relationship between the community and the aggressive child, one is apt to devote too much time to the problem of helping the already established delinquent child. Far more good will accrue to society if the psychiatrist will look further ahead, and will see the problem as one of positive

mental health by helping to uncover and to devise remedies for the social diseases which permit or encourage such unproductive aggression. This will be a much greater contribution than simply to approach the subject from the point of view of an exercise in salvage.

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THE EPHEDRINE TREATMENT OF NOCTURNAL ENURESIS.

By G. de M. Rudolf, M.R.C.P., D.P.M., D.P.H.,

Visiting Psychiatrist, Hortham Colony, Bristol; Hon. Psychiatrist, Bristol Clinic for Functional Nervous Disorders.

Treatments for enuresis have been legion, but several authors have recorded beneficial results from the use of ephedrine hydrochloride.

Table I.—*Summary from Literature.*

Author.	Numbers.	Ages in years.	Dose.	Additional treatment.	Remarks.
Parkhurst	..	10–12	½ gr. (·032 gm.)	Limitation of fluids	"Almost specific."
Christopherson and Broadbent	12	3–13	¼ gr. (·016 gm.)	..	8 controlled.
			½ gr. (·032 gm.)	Alk. belladonna	4 controlled.
Brookfield	32	Children	½–5 gr. (·032–·324 gm.)	..	10 ceased. 14 improved.
Browne and Ford-Smith	6	14–20	1–4 gr. (·06–·24 gm.)	..	3 better; 2 worse.
Stalker and Band	27	Adults	1½–3 gr. (·032–·194 gm.)	Limitation of fluids	8 ceased; 6, 75% improved; 6, 50% improved;
		Children	Less		3, 25% improved.
Kittredge and Brown	25	,,	¾ gr. (·049 gm.)	..	23 ceased.
Total	102				Improved 85 (83·4%)

Parkhurst's subjects urinated normally before and two hours after going to bed.

Christopherson and Broadbent report that of the 8 cases controlled by ephedrine gr. ¼ (·016 gm.), 7 were also controlled by gr. ½ (·032 gm.) pseudo-ephedrine hydrochloride, the eighth being controlled by gr. ¼ (·016 gm.). Of the four cases requiring gr. ½ (·032 gm.) of ephedrine with belladonna during the day, 2 required gr. 1 (·065 gm.) of pseudo-ephedrine with the belladonna and 2 only gr. ½ (·032 gm.) with the belladonna. One case improved with gr. ¼ (·016 gm.) pseudo-ephedrine, but responded completely to gr. ½ (·032 gm.). The treatment was given for from 1–4 months.

Brookfield found that months of persevering treatment were needed in certain cases before improvement occurred. Of his 17 males and 15 females, 4 of each sex failed to improve.

Browne and Ford-Smith expressed their results as a comparison with the total possible number of beds that could be wet. Consequently, their results express the number of nights wet, not the number of times that enuresis occurred. Their cases were wakened for urination two hours after going to sleep.

Stalker and Band measured the degree of improvement on a rough percentage scale.

First eliminating organic causes, such as infection of urine, mechanical obstruction to emptying the bladder with resultant retention, and neurological defect interfering with the function of the bladder, Kittredge and Brown gave the treatment for two weeks. Enuresis re-commenced in 11 cases. These authors state that the treatment must, probably, always be given for 3 weeks, and that nightly treatment for one month may be necessary before any improvement occurs. An increase above a dosage of gr. $\frac{3}{4}$ (·049 gm.) in cases of failure produced no additional benefit. These authors record one case, a man 23 years of age and incontinent since a child, who showed no recurrence during an observation period of four years after receiving gr. $\frac{3}{4}$ (·049 gm.) nightly for three weeks. A boy, aged 9, incontinent "practically every night," showed no enuresis during an observation period of three years following two courses of treatment of three weeks each. Two other illustrative cases, each with freedom of recurrence over six months, are those of a 17-year-old female, an enuretic since infancy, who received gr. $\frac{3}{4}$ (·049 gm.) for three weeks, and a $3\frac{1}{2}$-year-old boy who was given the same dose for one month. Enuresis ceased, but he was given an additional course of the same dosage for three weeks.

Present Investigation.

An investigation of the value of ephedrine in persistent nocturnal enuresis has been undertaken at Hortham Colony on a total of 90 resident mental defectives of both sexes and from 2 to 27 years of age. Although Kittredge and Brown found, by the use of sugar-coated pills substituted for the ephedrine, that suggestion plays no, or little, part in the treatment, the use of low-grade mental defectives was believed to reduce the effect of suggestion to negligible proportions.

Staff Supervision.

Clearly, the number of times that a case is found to be wet is related to the number of times that the nurse examines the sheets. For instance, a patient may wet the bed two or three times before the bed is examined, with the consequent result that one wet bed instead of two or three is recorded. The records of wet beds show the minimum and not the maximum number of times that the individual has passed urine. A good nurse who knows the patient at night will often be able to prevent a wet bed occurring by awaking the patient and causing him to micturate at the most advantageous times.

Instructions to the night staff, their knowledge of the cases and changes in staff may, in consequence, influence the results of investigations of treatment.

Investigations.

In the following investigations fluids were not restricted, but the cases were encouraged to micturate before going to bed and were awakened during the night. These practices were adopted before and during the test periods.

Test 1.—*Small Dose.*

Cases: 30 males, 12 females, from $2\frac{8}{12}$ to $18\frac{3}{12}$ years of age; 38 idiots, 2 imbeciles, 2 feeble-minded.

Incontinence: All incontinent every night.

Staff: All cases nursed by same staff. Instructed to record number of times wet nightly.

Dose: Gr. $\frac{1}{2}$ (·032 gm.) between 6 and 7 p.m. nightly for 4 weeks. Records for 3 weeks.

Test 2.—*Medium Dose.*

Cases: 17 males from $10\frac{8}{12}$ to $23\frac{9}{12}$ years of age; 11 idiots, 5 imbeciles, 1 feebleminded.

Incontinence: Observation for 2 weeks before treatment.

Staff: One nurse, who knew all cases thoroughly, during test.

Dose: Gr. $1\frac{1}{2}$ (·097 gm.) at 5–6 p.m. nightly for 12 weeks.

Test 3.—*Doses Varying from Low to High.*

Cases: 11 females from 17 to 26 years of age; 1 idiot, 9 imbeciles, 1 feeble-minded.

Incontinence: Observed for 2 weeks before treatment and continued for 2 weeks after cessation of treatment.

Staff: Accustomed to the cases. Instructed to examine frequently.

Dose: Gr. $\frac{3}{4}$ (·049 gm.) to gr. $2\frac{1}{4}$ (·146 gm.) nightly, from 6–7 p.m. for 16 weeks.

Test 4.—*Test of Effect Early or Late in the Night.*

Cases: 21 males, 12 females from $2\frac{2}{12}$ to $26\frac{11}{12}$ years of age. Twenty of these cases were not included in Tests 1, 2 and 3.

Incontinence: Not cured by ephedrine.

Staff: Instructed to examine cases before and after midnight.

Dose: Gr. 1 (·065 gm.) or 2 (·13 gm.) nightly for 8 to 11 nights.

Results.

Test 1.

During the test no alteration was made in the routine examination and raising of the patients. The results were recorded continuously during the first, second and third weeks of treatment in 21 males and 11 females, and during the first, third and fourth weeks in 9 males and 1 female.

The number of nights on which the cases were incontinent was, as compared with the period previous to treatment, reduced in 21 patients (50 per cent.) and stationary in 21 cases. Of the 30 males, 18 (60 per cent.) improved, but of the 12 females only 3 (25 per cent.) improved.

The number of times that each child was wet weekly decreased from the first week of treatment in 26 (61·9 per cent.) cases, remained stationary in 5 (7·1 per cent.) and became more numerous in 11 (26·2 per cent.).

Of the 30 males, 18 (60 per cent.) showed improvement, 4 (13 per cent.) remained stationary and 8 (27 per cent.) became worse. Of the 12 females, 8 (67 per cent.) improved, 1 (8 per cent.) showed no change and 3 (25 per cent.) deteriorated.

Only two patients, a feeble-minded boy, aged $6\frac{8}{12}$, and an idiot boy, aged $2\frac{1}{12}$, became completely continent during the three weeks of treatment. Two cases, an imbecile boy, aged $11\frac{6}{12}$, and a feeble-minded boy, aged $5\frac{4}{12}$, were completely continent for two of the three weeks.

Test 2.

In view of the failure of many cases to improve on the small dose given in Test 1, a test of three times the dose was carried out.

Although the nurse on duty throughout this test knew the patients well, no ephedrine was given for the first two weeks.

With regard to the number of times wet, 8 (47 per cent.) showed definite improvement, 3 (17·6 per cent.) showed doubtful improvement, 1 (5·9 per cent.) remained unchanged and 5 (29·4 per cent.) became worse. Only 2 cases became completely continent, both being so for one month of treatment. Of the 17 cases, 7 (41·2 per cent.) showed a decrease in the number of nights of incontinence, 2 (11·8 per cent.) showed a doubtful improvement, 7 (41·2 per cent.) showed no change and 1 (5·9 per cent.) became worse.

Six cases showed a marked temporary improvement, both with regard to the number of times incontinence occurred and to the number of nights on which incontinence took place. This temporary improvement persisted from 4 to 10 weeks after the commencement of the treatment. It occurred in cases who showed improvement at the end of the treatment, cases who remained stationary and those who had become worse by the end of the test period.

Test 3.

In this test no ephedrine was given for the first two weeks. During the third and fourth weeks gr. $\frac{3}{4}$ (·049 gm.) was given. At the beginning of the fifth week the dose was decreased to gr. $\frac{1}{2}$ (·032 gm.) in 5 cases and increased to gr. 1 (·065 gm.) in 6 cases. The doses were maintained at these levels during the sixth week. At the commencement of the seventh week all doses were increased by gr. $\frac{1}{4}$ (·016 gm.), and a similar increase was made at the beginning of the 9th, 11th, 13th and 15th weeks, a dosage of gr. $2\frac{1}{4}$ (·146 gm.) being given to 6 cases during the 15th and 16th weeks. No treatment was given during the 17th and 18th weeks.

With regard to the number of nights on which wet beds occurred, 2 imbeciles showed no improvement on any of the doses given, these two reaching a dosage of gr. $2\frac{1}{4}$ (·146 gm.). The remaining 9 cases improved, one for 12 weeks only and another for 8 weeks only, in spite of the continuance of the ephedrine. Seven cases (63·5 per cent.) maintained their improvement even during the final two-week period with no treatment.

The number of times that wet beds were found decreased in every case, although in the two imbeciles showing no improvement in the number of

nights wet, the reduction lasted for 12 and 14 weeks only. In a third case, an idiot, the improvement ceased after the cessation of the treatment. In the remaining 8 cases (one died earlier) the improvement persisted during the two weeks following the termination of the treatment, although the degree of improvement became less. No case became worse.

The increase of the dose, up to twice its initial strength, did not increase the improvement obtained with the initial smaller dose, either as regards the number of wet beds or the number of nights on which wet beds occurred.

Test 4.

In Tests 1, 2 and 3 the ephedrine was given in the evening between 5 p.m. and 7 p.m. It was thought that, possibly, in cases who failed to react satisfactorily, the incontinence might have occurred late in the night only. In consequence a second dose given after midnight might be of benefit.

The total of 33 cases gave 181 wet beds before midnight and 266 after midnight during the periods of observation, which were the equivalent of 322 nights for one patient. If the duration of the effect varied with the dose, then the cases receiving gr. 2 (·13 gm.) should show a smaller proportion of wet beds after midnight than should those receiving half this amount. Table II shows that this is not so. In fact, the ratio is greater in the cases receiving the higher dose.

TABLE II.—*Varying Dosage and Time of Enuresis.*

1. Dose	gr. 1 (·065 gm.)	gr. 2 (·13 gm.)
2. Number of cases	26	15
3. Wet beds before midnight	126	44
4. Wet beds after midnight	176	85
(4)/(3)	1·4	1·9
Hours After MN / Before MN	2	2

When a comparison is made on the same patients, first receiving gr. 1 (·065 gm.) and later gr. 2 (·13 gm.), similar results are obtained. Table III shows a comparison on 8 cases extracted from Table II. The cases were given gr. 1 (·065 gm.) for a period equivalent to 1 case over 48 nights and gr. 2 (·13 gm.) equivalent to 1 case over 35 nights. The Table shows that the proportion of wet beds after midnight is higher with the larger dose.

TABLE III.—*Same Cases given first gr.* 1 (·065 *gm.) and later gr.* 2 (·13 *gm.*).

1. Dose	gr. 1 (·065 gm.)	gr. 2 (·13 gm.)
2. Wet beds before midnight	20	12
3. Wet beds after midnight	43	32
(3)/(2)	2·15	2·67

The greater number of wet beds after midnight in Tables II and III could be due to a disproportion in the hours before and after midnight during which the night staff were on duty. The nurses were on duty for four hours before midnight and eight hours after, the proportion of 1 to 2 resembling the ratio between wet beds before midnight and wet beds after midnight.

Sheets.

In Test 2 a record was kept of the number of sheets wet and sent to the laundry. A definite decrease occurred (Table IV).

TABLE IV.—*Sheets Sent to Laundry.*

	Fortnightly periods.					
Pre-treatment.	1st.	2nd.	3rd.	4th.	5th.	6th.
211	132	81	128	138	133	145

Temperature.

The frequency of micturition is commonly stated to be related to the atmospheric temperature. As an alteration in temperature might have influenced the results of the three tests, the nightly dormitory temperatures at midnight and at 4 a.m. for the cases of Test 2 were averaged, the means for each fortnight being shown in Table V. These means are the means of the mean midnight and 4 a.m. temperatures of each night and averaged for each fortnightly

TABLE V.—*Total Wet Beds for Series of 17 Male Defectives.*

Periods 1–6 = October to February; 1–4 = April to May; A–D = July to August.

	Fortnightly periods of treatment.													
	1.	2.	3.	4.	5.	6.	1.	2.	3.	4.	A.	B.	C.	D.
Mean temp.	48·4	46·5	44·5	46·5	46·9	42·1	50	51·3	52·7	57·8	58·4	63·8	61·3	64·
Number of nights wet	79	70	87	106	103+	116+	106	96	95	74	121	115	106	13
Number of times wet	84	82	122	138	128+	142+	145	142	142	118	154	141	144	17

+ = one patient excluded from series as in hospital.

period. The Table shows that when the higher dormitory temperatures occurred not only did no reduction of wet beds take place, but an actual increase was noted. The rise in dormitory temperature did not, therefore, influence the test results favourably.

Mode of Action.

Parkhurst, and Kittredge and Brown, point out that ephedrine contracts the trigone and relaxes the fundus of the bladder. The last two writers add that it activates the internal sphincter, inhibits the detrusor muscle and contracts the ureteral orifices.

This action would be anticipated to prevent urinary incontinence whether the origin were psychological or physical, and make the causation of the enuresis of little therapeutic interest. Although Kittredge and Brown excluded organic causes before commencing treatment, this was not done in the present series, the actions of the ephedrine being assumed to be on the bladder as described by Kittredge and Brown. If ephedrine acts on the terminal end-organ of micturition, the organs initiating the bladder's action are of no moment from a therapeutic aspect.

Discussion.

Table VI shows the results obtained in the tests according to changes in the number of nights in which incontinence occurred. The final column, "Worse," is of little value, as it is clear that if a patient, before treatment, was incontinent every night, as was the case with most patients, he or she could not become worse.

Table VI.—*Nights in which Incontinence Occurred.*

Test.	Cases.	Sex.	Dose (gr.).	Improved.	Doubtful and no change.	Worse.
1	42	M. & F.	½	20 (47·6%)	21	0
2	17	M.	1½	7 (41·2%)	9	1
3	11	F.	¾–2¼	9 (81·8%)	2	0
	70			36	32	1

Table VII shows the results according to the number of times each case was incontinent. A few of the improvements, as noted in the descriptions of each test, were temporary in character.

Table VII.—*Number of Times of Incontinence.*

Test.	Cases.	Sex.	Dose (gr.).	Improved.	Doubtful and no change.	Worse.
1	42	M. & F.	½	26 (61·9%)	5	11
2	17	M.	1½	8 (47·0%)	4	5
3	11	F.	¾–2¼	11 (100%)	0	0
	70			45	9	16

The tests, especially Test 3, showed that results were better with a dose of gr. ¾ (·049 gm.) than with gr. ½ (·032 gm.), but that a dose exceeding gr. 1 (·06 gm.) gave no further improvement.

The markedly higher percentage of improvement in Test 3 as compared with Tests 1 or 2 cannot be due to all the cases being females, for in Test 1 the percentage of improvements for the number of nights incontinent was 60 for the males and 25 for the females, and for the number of times incontinent 60 and 66 respectively. If the sex affected the results the rates in Table VII should be less for Test 3 than for Test 2, not more. The differences may

perhaps be due to the differences in the mental grade of the cases. These are shown in Table VIII. In Test 3 the proportion of idiots was lower than in the other tests.

TABLE VIII.—*Mental Grade of Patients.*

Test.	Total.	Idiots.	Imbeciles.	Feeble-minded.
1	42	38 (90·5%)	2	2
2	17	11 (65%)	5	1
3	11	1 (9·1%)	9	1

If the mental grade were the sole factor in the differences in the rates of improvement, then the idiots should show a lower improvement rate than the imbeciles and feeble-minded. This is shown in Table IX.

TABLE IX.—*Improvement of Each Mental Grade.*

	Number.	Improved nights.		Improved times incontinent.	
Idiots	50	17 (34%)		27 (54%)	
Imbeciles	16	10 (62·5%)	70%	13 (81·2%)	80%
Feeble-minded	4	4 (100%)		3 (75%)	

These figures, however, include those idiots who were given the small doses of Test 1. If the idiots who received the larger doses in Tests 2 and 3 are compared with the imbeciles and feeble-minded who received the same dose, it will be seen that idiots reacted less favourably to ephedrine than did higher grade defectives (Table X).

TABLE X.—*Improvement and Mental Grade.*

	Number.	Improved nights.	Improved times.
Idiots	12	5 (41·7%)	7 (58·1%)
Imbeciles and feeble-minded	16	10 (62·5%)	13 (81·2%)

The age of the case treated may be related to the success or failure of the treatment. Table XI shows the age-groups.

TABLE XI.—*Improvement in Age-Groups.*

Ages (years).	Number.	Improved nights.	Improved times.
0–	31	14 (45·2%)	19 (61·3%)
10–	25	10 (40·0%)	14 (56·0%)
20–27	15	10 (66·7%)	11 (73·3%)

It is of interest that, although the numbers are small, the greatest improvement occurred in the oldest group, and that this group contained approximately the same proportion of idiots as the age-group below. The increase in the improvement rate cannot therefore be due to a higher proportion of

idiots (see Table XII), and is presumably connected with the actual chronological age of the cases.

TABLE XII.—*Ages and Classifications.*

Ages (years).	Idiots.	Imbeciles.	Feeble-minded.	Total.
0–	29 (90·7%)	1 (3·1%)	2 (6·2%)	32
10–	14 (58·3%)	8 (33·3%)	2 (8·3%)	24
20–27	7 (50·0%)	6 (42·8%)	1 (7·1%)	14
				70

By comparing the condition before treatment with the greatest improvement after the commencement of treatment, the degree of improvement can be obtained, even if this is of a temporary nature only.

TABLE XIII.—*Degree of Improvement. Number of Nights Wet per Week.*

Dose (gr.) :—	½.	¾.	1¼.	1½.
	Number of cases.			
	44.	10.	1.	16.
Percentage of improvement. 100%	6	8	1	9
90	0	0	0	0
80	1	0	0	3
70	4	0	0	1
60	0	0	0	0
50	2	0	0	0
40	0	0	0	1
30	3	0	0	0
20	2	0	0	2
10	9	1	0	0
0	17	1	0	0

TABLE XIV.—*Degree of Improvement. Number of Times Wet per Week.*

Dose (gr.) :—	½.	¾.	1¼.	1½.
	Number of cases.			
	1.	10.	1.	16.
Percentage of improvement. 100%	0	8	1	9
90	0	0	0	0
80	0	0	0	3
70	0	0	0	1
60–50%	1	0	0	1
40	0	2	0	1
30	0	0	0	0
20	0	0	0	0
10	0	0	0	1

Tables XIII and XIV show the maximum degree of improvement obtained, the immediate pre-treatment fortnight being taken as the standard for comparison.

The known duration of the improvement is partly dependent upon the periods of observation. The maximum improvement did not invariably persist to the end of the observation period, although improvement of a lesser degree may have done so.

TABLE XV.—*Cases in Which Maximum or Total Improvement in Number of Nights Wet, and Times Wet in Brackets, was Present at Termination of Period of Observation.*

	Cases.	Duration of observation (weeks).	Maximum improvement.	Total improvement.
Test 1	27	3	12	21
Test 2	17	12	5 (5)	10 (11)
Test 3	10	16	1 (1)	8 (9)

This table shows that the maximum degree of improvement does not invariably persist for any great length of time, either with regard to the number of nights on which enuresis occurred or to the total number of times wet. On the other hand, improvement of some degree persisted to the end of the period of observation in most patients, in from 59 to 80 per cent. of cases.

TABLE XVI.—*Number of Cases in Whom Improvement (Nights Wet) Occurred in Tests 1, 2, and 3, with Length of Improvement in Weeks. + = Persisting to End of Observation.*

	Weeks.	1.	2.	3.	1+.	2+.	3+.
Test 1.	*Maximum imp.*	13	2	0	7	3	2
	Total imp.	4	2	0	5	6	10

	Weeks.	0–3.	4–6.	7–9.	10–12.	13–16.
Nights wet	*Test 2 max. imp.*	8	3	1	0	—
	Test 3 max. imp.	4	3	2	0	0
	Test 2 total imp.	1	3	3	0	—
	Test 3 total imp.	1	0	0	1	0

TABLE XVII.—*Number of Cases in Whom Complete Durations of Improvements were Recorded.*

	Durations in weeks.	0–3.	4–6.	7–9.	10–12.	13–16.
Times wet	*Test 2 max. imp.*	7	3	1	0	—
	Test 3 max. imp.	5	3	2	0	0
	Test 2 total imp.	3	2	1	0	—
	Test 3 total imp.	0	0	0	0	2

TABLE XVIII.—*Number of Cases in Which Improvement Persisted to End of Observation, with Duration of Improvement in Weeks.*

	Duration in in weeks.	0–3+.	4–6+.	7–9+.	10–12+.	13–16+.
Nights wet	Test 2 max. imp.	0	1	3	1	—
	Test 3 max. imp.	0	0	1	0	0
	Test 2 total imp.	1	1	4	4	—
	Test 3 total imp.	0	0	0	0	8
Times wet	Test 2 max. imp.	0	1	3	1	—
	Test 3 max. imp.	0	0	1	0	0
	Test 2 total imp.	1	0	4	6	—
	Test 3 total imp.	0	0	0	0	9

These tables show that improvement may not occur until the ephedrine has been given for from 9 to 11 weeks, although such a long delay is unusual. A delay of approximately a month before improvement occurred was common.

Ephedrine was given continuously to the cases of Test 3 for one year. After about 8–9 months of treatment the numbers of cases showing improvement decreased (Table XIX), the numbers of those becoming worse or showing no change increased. It may, therefore, be that ephedrine should be given intermittently, and that too great a length of dosage may reduce the earlier beneficial results.

TABLE XIX.—*Continuous Treatment for One Year.*

A = October to February; B = April to May; C = July to August.

Periods.	Nights wet.			Times wet.		
	A.	B.	C.	A.	B.	C.
Improved	7	9	5	8	10	5
Doubtful	2	4	2	3	2	1
No change	7	3	7	1	0	5
Worse	1	1	3	5	5	6

CONCLUSION.

1. Ephedrine hydrochloride improved nocturnal enuresis in approximately 40–60 per cent. of mental defectives, but made some cases worse.

2. The improvement was of considerable duration in from 66 to 75 per cent. of cases.

3. An oral dose of approximately gr. 1 (·065 gm.) was required nightly for children and adults. Higher doses did not produce greater improvements.

4. A rise in the dormitory temperature did not decrease the total number of wet beds.

5. The number of sheets sent to the laundry decreased.

6. Higher-grade cases reacted more favourably than did lower-grade defectives.

7. Older patients showed a higher improvement-rate than did the younger.

8. With adequate dosage, the degree of improvement in each case was usually from 80 to 100 per cent.

9. Although improvement persisted to the end of the observation periods (i.e. for 3 and 4 months) in about 75 per cent. of the cases, the maximum improvement persisted for this length of time in only 25 per cent. of the cases.

10. Improvement did not commence until approximately 3 months after the beginning of the treatment in one case. The majority of improvements commenced before the end of one month.

11. The numbers of cases maintaining their improvement when ephedrine was given continuously decreased after 8 or 9 months, so intermittent dosage, as for a month with monthly intervals, may be more advantageous.

In conclusion, my thanks are due not only to Dr. J. F. Lyons, Medical Superintendent of Hortham Colony, for permission to carry out these investigations, but also to Chief Male Nurse H. T. Hills and Sister E. M. Walker, who were responsible for the excellent keeping of the numerous records required.

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FURTHER ASPECTS OF BRIEF RETROGRADE AMNESIA.

G. de M. Rudolf, M.R.C.P., D.P.M., D.P.H.,

Lately Specialist Psychiatrist, R.A.M.C.; Visiting Psychiatrist, Mount Pleasant, Clevedon; Hon. Psychiatrist, Bristol Clinic for Functional Disorders.

Knowledge of amnesia is dependent upon the subject's statement. He can tell us what he will. If he has studied the subject well, he can mislead us. He may have motives for fabricating. He may benefit, he thinks, financially, socially or in other material ways, by inventing an amnesia. A history of grave injury may produce avoidance of danger or of unpleasant work. A medical history, which the patient may think unusual, may give him prestige or sympathy. Finally, he may invent an amnesia to give the doctor a good story or to "pull his leg."

Comparison of Cases.

In view of these possibilities of error in the descriptions of R.A., a comparison between two types of cases examined by the same psychiatrist has been made.

The first type of case consisted of candidates for officer-training at a War Office Selection Board, commented upon previously (Rudolf, 1947). These subjects would desire to appear at their best when interviewed by the psychiatrist. Conscious exaggeration of amnesia would be unlikely.

The second type of case consisted of men receiving pensions from the Ministry of Pensions, examined from 1 to 29 years after the injuries or incidents had occurred. As the possibility existed that the reporting of R.A. might be related to the state of the mind before the occurrence of the injury or incident, the cases were divided into three groups:

(*a*) Those in whom thoughts of danger had been present for at least one minute before the incident;

(*b*) those in whom thoughts of danger were unlikely to have been present for more than a few seconds preceding the incident; and

(*c*) those in whom no thought of danger, even for the briefest of periods, could have been in existence prior to the incident or injury.

Group (*a*) consists largely of incidents and injuries occurring during action or air-raids. Group (*b*) consists largely of road accidents, in which the subjects would usually not be thinking of danger, unless "nervous" of transport or of the particular driver. Group (*c*) consists of accidents which took place without even the shortest of warnings. All accidents which the subjects might conceivably have been anticipating were excluded from this group.

Table I shows that the W.O.S.B. and M. of P. subjects gave similar statements in Group (*c*), but widely differing ones in Groups (*a*) and (*b*).

TABLE I.—*Total Cases and Percentage of Retrograde Amnesia (R.A.) in brackets in W.O.S.B. and M. of P. Cases.*

	W.O.S.B.	M. of P.
Group (*a*)	50 (16·0)	78 (48·7)
,, (*b*)	27 (66·7)	35 (77·2)
,, (*c*)	22 (72·7)	11 (72·7)

The cause of the differences in Groups (*a*) and (*b*) might be related to the occurrence of unconsciousness or post-traumatic amnesia (P.T.A.) (see Table II).

TABLE II.—*Total Cases and Percentage of R.A. in brackets without P.T.A. and with P.T.A. in Groups* (a) *and* (b) *of W.O.S.B. and M. of P. Cases.*

	W.O.S.B.	M. of P.
Group (*a*) :		
No P.T.A. . . .	45 (15·5)	24 (25·0)
P.T.A.	5 (20·0)	54 (59·3)
Group (*b*) :		
No P.T.A. . . .	10 (30·0)	5 (40·0)
P.T.A.	17 (88·2)	30 (83·3)

In Group (*b*) the proportions of R.A. amongst both the W.O.S.B. and M. of P. cases are very similar. As in the M. of P. cases of Group (*a*) the proportion of R.A. amongst the cases with P.T.A. is greater than amongst those without it.

The relative equality of the proportion of R.A. in both the No P.T.A. and P.T.A. classes of the W.O.S.B. series of Group (*a*) is the exception in both Groups (*a*) and (*b*). The low proportion of R.A. in the P.T.A. cases is very striking.

In view of the markedly higher proportion of R.A. in the P.T.A. cases in both the W.O.S.B. (Group *b*) and M. of P. cases (Groups *a* and *b*), it is most probable that both the W.O.S.B. candidates and the M. of P. pensioners did not falsify their experiences.

The table shows that in Group (*a*) W.O.S.B. cases, the presence of R.A. is not related to the presence of P.T.A., approximately equal percentages of cases occurring amongst those without, and those with, P.T.A. In the M. of P. cases the situation is very different. In the cases without P.T.A. the proportion of M. of P. cases with R.A. is slightly greater than in the W.O.S.B. series, but the proportion of R.A. cases amongst those with P.T.A. is three times as great as in the W.O.S.B. cases.

Tables III and IV, dealing with cases of Groups (*a*), (*b*) and (*c*) together, show that R.A. is remarkably similar in cases with P.T.A. amongst both the M. of P. and the W.O.S.B. series. In the cases without P.T.A. or unconsciousness, its presence is more common in the M. of P. cases than in the W.O.S.B. group. As the percentages are similar in Table III, it would again be unlikely that the subjects of Tables III or IV had been deliberately falsifying

their statements. Table IV must represent a real difference, and shows R.A. is more common amongst non-P.T.A. cases in the M. of P. series than amongst the same cases in the W.O.S.B. group. As judged by the above tables, the assumption can be made that the majority of W.O.S.B. and of M. of P. cases did not falsify their actual beliefs of the presence of R.A., unless, perhaps, some of the W.O.S.B. cases of Group (*a*) with P.T.A. deliberately omitted to report the R.A. The possibility exists that, as these candidates would wish to show themselves at their best, they would have not reported R.A., but if so, there appears to be no reason why the candidates of Groups (*b*) and (*c*) should have reported their R.A. If some candidates believed that their acknowledgment of the presence of R.A. would militate against their selection for officer-training and consequently hid its existence, why should its presence be acknowledged in proportions resembling those of the pensioners in Groups (*b*) and (*c*) ?

TABLE III.—*Cases with P.T.A. (i.e. Unconscious after Injury or Accident). (Percentage of Cases with R.A. in brackets.)*

	Total cases.
M. of P.	85 (71·8)
W.O.S.B.	33 (75·8)

TABLE IV.—*Cases not Unconscious after Injury or Incident. (Percentage of Cases with R.A. in brackets.)*

	Total cases.
M. of P.	40 (55·0)
W.O.S.B.	66 (27·3)

RETROGRADE AMNESIA WITHOUT P.T.A. OR CONCUSSION.

In a previous article (Rudolf, 1947) attention was drawn to the occurrence of amnesia when accidents are anticipated by the subject but do not, in fact, occur, as in parachute-jumping. Other types of cases are quoted below :

1. Officer buried in dug-out by blockage of exit by earth. Amnesia for 4 hours, still present 26 years later, although subject was not injured in any way whatsoever.

2. Woman, aged 72 years, in shop that caught fire in her presence. Amnesia from time of the entrance of two boys who came to help to extinguish the fire until on couch, after fire extinguished, holding a cup of tea and saucer in a tremulous hand. With the exception of slight singeing of the hair of the head, no injury was sustained.

3. Woman, aged 20 years, in A.T.S. Amnesia for accident occurring 1½ years previously. Recalled seeing bus approaching her and nothing further until she was standing up on the road, leaning forward with blood coming from face. Informed was not unconscious. The sole injury sustained was a cut on the right cheek. Hypno-analysis, conducted over numerous sessions, recalled to her memory riding down a hill on her bicycle, seeing the rear of a lorry in front of her, looking down to ensure that shoes she was carrying were not slipping out of her hand on the handle-bar, looking up and seeing that lorry was much nearer, realizing inability to pull up, swerving around outer side of lorry, seeing bonnet of approaching bus in front of her, realizing there was sufficient space for her to pass between bus and lorry, but feeling body paralysed and mind unable to compel it to act appropriately. She recalled the mirror projecting from the lorry, the windows of the bus flashing

past her, seeing front wheel of her bicycle striking the bus, being thrown up from the seat of the bicycle with her left arm beside her face, head striking something that gave way, sound of glass breaking and sensation of falling through the air to the ground.

4. Woman aged 71 years. Amnesia for falling downstairs 5 years previously. Was able to recall commencement of turning over at the top of the stairs and then sitting at the bottom, and noticing that a picture on the wall, half-way down the stairs, was hanging crooked. Under hypno-analysis, conducted over 15 sessions of approximately 30 minutes each, recalled falling in space, sound resembling that of turning on an electric light by means of a chain, passing picture hanging straight on the wall, palmar surface of fingers of right hand striking picture, falling head first with face uppermost, fearing might crash into the hall-stand, knocking toes of one foot, hearing a thud, sliding down the lowest two or three stairs with her head towards banisters and feet towards wall, knocking right elbow on, probably, the bottom stair, bending trunk, striking back of head and left buttock simultaneously, and being in sitting position with back against pillar of the lowest banister. The fall was caused by the subject taking a step sideways over the edge of the top stair in the dark of the black-out. An electric lamp, with a chain attached, hung over the landing at the head of the stairs. She believed, although not absolutely certain, that, as she began to fall, her left hand pulled the chain. As the subject saw the picture on the wall as she passed it, some illumination must have been present.

If, in either case 3 or 4, the head had been struck more violently and concussion had occurred, the amnesia would have been termed retrograde. The fact that concussion did not take place was only incidental, the amnesia being present even without the occurrence of so-called P.T.A.

The Abolition of R.A.

Nathan (Russell and Nathan, 1946) administered barbiturate narcosis to 40 patients recovering from head injury. The method consisted of giving one injection to each man, accompanied by the customary questioning and "during the following week or months he would be questioned again from time to time." With this method, "some additional memory in the R.A. period was recovered in 12 cases, although this was sometimes insignificant."

My own experience confirms Nathan's findings of poor results. To recover the memory completely, hypnosis is necessary on many occasions. Simple questioning after one period is quite insufficient. I find that at least six sessions of hypnosis, each of approximately 30 minutes in duration, are required to recall all the memories, including those of the most alarming moments. Often a total of 5 or 10 hours of hypnosis is needed. A total of a few hours may recall a few memories or even nothing.

However, occasionally the R.A. can be reduced with the type of short therapy used by Nathan, who reports one case in which the R.A. was reduced from 30 minutes to *nil*, and three others in which it was reduced to a moment from 2 hours, 20 minutes and a few seconds respectively. In these cases the hypnosis was performed, at the latest, two months after the injury.

Guttmann (1946) has recorded that R.A. may shrink for months after an injury, and Russell and Nathan (1946) report two cases of this occurrence. The first case showed an R.A. of 7 years' duration, one week after the accident, but 9 weeks later this had reduced itself to a few minutes. In the second case, an R.A. of 6 months in duration, present $3\frac{1}{2}$ months after an injury, had

shortened to a few minutes one month later. A third instance, my own, consisted of the gradual disappearance of an amnesia preceding the explosion of a bomb 7 yards distant. Two weeks after the incident a full and complete memory had returned without treatment. No injury of any kind occurred. In view of these natural reductions or disappearance of the R.A. during the months following an incident, the results of therapy cannot be assuredly due to the treatment if it is given before the expiration of a year from the event.

The natural disappearance of R.A. can be readily studied in patients immediately after receiving electric-convulsive therapy. As the patient gradually and progressively recalls more and more of the period immediately preceding the passage of the current, the bewilderment passes, the expression becomes more full of meaning and, finally, all is recalled, including the placing of the electrodes upon the head. No abreaction or evidence of fear is observed during this recall of the memory. The memory returns calmly. This calm return of the memory, without any emotional sensation, was experienced by myself during the fortnight succeeding the explosion of the near-by bomb.

The conditions are very different during the recall of a terrifying experience. As the memory is recalled, no signs of fear appear until the approach of the moment of expectation of greatest danger. Then alarm may be marked. Flushing, palpitation, tremor and agonized facies may all be seen. Sweat may break out on the brow, and cries of fear, and terror-stricken shouting may be heard. Violence and fighting have been recorded.

The Causation of R.A.

As pointed out by Russell and Nathan (1946), R.A. can be organic in origin. These authors refer to its occurrence after electric-convulsion therapy, status epilepticus, meningitis, acute cerebral anoxia, as in hanging, CO poisoning and severe loss of blood. It occurs in air-crew after a tight turn when body tissues increase in weight (Matthews, 1945), and Donald (1947) reports its occurrence for the post-convulsive automatism, covering periods up to 7 hours in duration, observed in experimental oxygen poisoning.

Although many cases of R.A. are organic in nature, many others are of psychological origin. Russell and Nathan (1946) point out that one "type of case bears a remarkable resemblance to the behaviour of a repressed complex in that an experience which had been registered and retained was not recalled except through an association of ideas, and this experience caused an emotional response which was appropriate to the forgotten material."

Not only does this type of case bear a resemblance to a repressed complex, but, in my experience, it is an instance of repression, this being due to intense fear, accompanied, possibly, by strong feelings of guilt.

The failure to obtain any recall of memory in 34 cases and of complete recall in 6 cases made Russell and Nathan (1946) report that their investigations with barbiturate hypnosis "provide confirmation of the view that both the R.A. and the P.T.A. in most cases is the result of physical effect of injury on brain neurones."

If the neurones are injured, how can they recover to produce a detailed account of the previously forgotten incidents from a few days to many months after the incident? The coincidence would be remarkable if oedema or other temporary impairment of neurone function should disappear from causes other than psychological during psychological treatment, even without the aid of barbiturates or other drugs, as much as 30 years after the amnesia-producing incident.

Guttmann (1946) points out that failure to remove the amnesia does not prove the organic nature of the condition, adding that real experiences or inhibitions may be concealed, even under sodium amytal.

Sargant and Slater (1941) suggest that the very brief period of amnesia which consists of the period immediately before a blow on the head, and which sometimes cannot be recalled under hypnosis, is due to organic causes. If so, it may be similar to that occurring during a tight turn in the air and other physical and chemical disturbances. However, it is very possible that the failure, which occurs in the exceptional case only, to recall the actual blow and the immediately preceding fraction of a second, may be due to imperfect technique. In the majority of cases, providing sufficient time is spent on each case, the complete period, including the blow, can be fully recalled.

Russell and Nathan (1946) describe cases showing that the retention of recent memories is less firmly established than is that of earlier ones. Although, in most cases, the last event recalled under hypnosis has been the blow causing unconsciousness, I have seen one instance (Rudolf, 1947, case 24) in which the last event recalled under hypnosis was not the last event in order of time before unconsciousness occurred. In another instance (Rudolf, 1947, case 25), an untreated patient, the amnesic period covered a brief period before he struck the ground. The memory of the last event, striking the ground, was not repressed or destroyed.

Without treatment the amnesic gap appears to be shortened from the more remote period. Under hypnotic treatment of many sessions the gap can be closed from either end, but the moment of greatest terror, which is usually at the more recent end, is the last event to be recovered. During the recovery of any memory not associated with fear, no abreaction is seen. The items are merely quietly remembered. The organically-produced amnesia causes no abreaction as it disappears, but that psychologically produced shows abreaction as the moments of fear are approached and reached. In many cases the organic amnesia fades, leaving the psychological amnesia, which cannot be abolished unless prolonged treatment is performed. This difference in the emotion associated with recall is the significant, and perhaps the sole, difference between the two causally-dissimilar amnesias.

Symptoms

In 104 M. of P. cases examined from $1\frac{1}{2}$ to 29 years after injuries or terrifying incidents, a total of 38 different symptoms were described. The number of cases, either with or without R.A., who reported symptoms are

shown in Table V, symptoms reported by less than 6 patients being omitted. This table shows that depression, irritability, sweating and poor memory were described less frequently amongst the cases without R.A. than amongst those with it. Tremor, nightmares, insomnia and giddiness, were more common amongst cases without R.A. than amongst those with it. Consequently, cases with R.A. tend to complain of depression, irritability, sweating and poor memory. Cases without R.A. tend to report nightmares, insomnia and giddiness, and to show tremor.

TABLE V.—104 *Cases Reporting Symptoms.* (*Percentages in Brackets.*)

Symptoms.	With R.A. (63).	Without R.A. (41).
Depression	14 (22·2)	5 (12·2)
Poor memory	10 (15·9)	4 (9·8)
Irritability	7 (11·1)	3 (7·3)
Sweating	6 (9·5)	3 (7·3)
Nightmares	15 (23·8)	14 (34·1)
Giddiness	12 (19·0)	11 (26·8)
Tremor	10 (15·9)	8 (19·6)
Insomnia	8 (12·7)	10 (24·4)
Headache	43 (68·2)	25 (61·0)
Pains elsewhere	8 (12·7)	5 (12·2)
Poor concentration	6 (9·5)	4 (9·8)

Although a higher proportion of cases with symptoms record R.A. than do those without important symptoms (Table VI), Yule's co-efficient of correlation for symptoms and R.A. is only + ·369.

TABLE VI.—*Symptoms Causing Interference with Normal Activity and R.A.*

	Number.	R.A.
Cases with symptoms (M. of P.)	125	61·2%
Cases without symptoms (W.O.S.B.)	99	42·6%

If the W.O.S.B. candidates who had undergone terrifying incidents and who were in Medical Category A1, that is, those individuals who were regarded as being completely physically fit, are divided into two groups, Table VII is obtained.

TABLE VII.—*W.O.S.B. Candidates. Minor Symptoms Insufficient to Warrant Med. Cat. below A1.*

	Number.	R.A.
Cases with minor symptoms	31	11 (37·0)
Cases without minor symptoms	41	16 (39·0)

The cases with symptoms are those who recorded presence of symptoms in reply to a question on the Questionnaire asking for an account of minor ailments. The table shows that the percentage of cases with R.A. is similar

in the cases with, and in those without, symptoms. The symptoms were, of course, not sufficiently serious to interfere with full activity.

Although patients may present symptoms for a considerable time, such as the two who had each complained for 29 years, occasional individuals show a slight and gradual improvement without treatment. Examples are of a man who showed R.A. with reference to falling to a lower deck three years ago. Headaches and nightmares occurred for one year, but during the past two years, the nightmares have been absent. A second instance is the case of a man who sustained concussion with R.A. when diving two years ago. Although the head pain and slow cerebration persist, the memory for day-to-day events is now improving. A third patient, four years ago, met with a road accident, causing concussion and accompanied by R.A. Giddiness still occurs, but headaches ceased one year after the injury. In view of the fact that anosmia following concussion may disappear many months, or even a year, after the damage, the cessation of the headaches might have been due to organic improvement.

Although the symptoms to which reference is made here are assumed to be caused by the injuries or incidents, this assumption is not necessarily correct. Guttmann (1946), in dealing with the late effects of closed head injuries, found that the incidence of one symptom, namely headache, is no greater amongst men who have received head injuries than amongst those who have not. This author obtained his results from an Officers' Board of the N.F.S., so that his figures are comparable with the W.O.S.B. cases rather than with those of the M. of P. group. The figures of Table VII are in agreement with Guttmann's findings, headache and pain elsewhere being in approximately similar proportions in the cases with R.A. and in those without this condition.

Summary.

1. Cases who were likely to wish to appear at their best (i.e. W.O.S.B. candidates) and cases in whom similar motivation was probably not present (i.e. pensioners) reported similar proportions of R.A. for incidents occurring when they were probably not thinking of danger, whether or not unconsciousness had occurred after injury or terrifying incidents.

2. The two series of cases gave different proportions of R.A. for incidents occurring when they were likely to be thinking of danger, i.e. when danger had existed for at least one minute before the incident, the difference being greatest amongst the cases recording P.T.A.

3. When all cases were considered, the percentages of R.A. were similar in the two series when P.T.A. had occurred, but dissimilar when it had not taken place, the M. of P. cases recording 55 per cent. of R.A. but the W.O.S.B. series recording only 27·3 per cent.

4. Attention is drawn to the occurrence of amnesia with anticipated, but not actual, accident, and to R.A. preceding accidents without P.T.A. or concussion.

5. The complete abolition of R.A. by hypnosis requires from 3 to 10 hours. As the R.A. often shrinks over a period of months without treatment, any

reduction of its length under one year from the precipitating incident may be due to the natural shrinkage rather than to the treatment.

6. The difference between R.A. due to structural, organic causes and that due to psychopathological causes appears to be that the first decreases and may disappear without the occurrence of abreaction, whereas abreaction occurs when the second is decreased or abolished.

7. Under hypnosis, any memory, whether distant or recent, can be recalled first, but the most terrifying memory, even if the most recent, is recalled last.

8. Cases with symptoms insufficient to affect appreciably the health do not record a preceding R.A. in greater numbers than do those without such symptoms.

9. Cases with symptoms affecting the subjects so greatly that pensions have been granted record an R.A. in greater proportions than do W.O.S.B. candidates without such symptoms.

10. Depression, irritability, sweating and poor memory were more common amongst cases with R.A. than amongst those without it. Nightmares, insomnia, giddiness and tremor were more common in cases without R.A. than amongst those recording this condition.

11. Although uncommon, a slow decrease of symptoms may occur as the years pass.

My thanks are due to Dr. E. Casson for permission to quote cases from Mount Pleasant Nursing Home, Clevedon.

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SOME CLINICAL OBSERVATIONS ON THE PSYCHODYNAMIC RELATIONSHIP BETWEEN DEPRESSION AND OBSESSIVE-COMPULSIVE SYMPTOMS.*

By E. Stengel, M.D.Vienna, L.R.C.P.Edin.,
Director of Clinical Research, Graylingwell Hospital, Chichester.

Obsessional symptoms and depression often co-exist. There are obsessional neurotics who are subject to recurrent depressions, and there are patients with marked obsessional personality features, but not suffering from an obsessional neurosis, who develop severe obsessional symptoms in the course of their depressions only. I do not agree with those writers who maintain that the typical features of the obsessional character can be found in every case of manic-depressive illness.

The study of the interaction between obsessional and depressive symptoms gives rise to a number of problems. The following two questions are of particular importance to the psychiatrist interested in psychodynamics: What is the fate of the obsessive-compulsive symptoms in the course of the depression? And secondly, does depression occurring on the background of obsessional neurosis differ from the typical depressive state? The most striking feature in many of those cases is the exacerbation of the habitual obsessive-compulsive symptoms during the depression and the emergence of new ones, usually with overt obsessive-destructive contents. The impulses are, during the course of the depression, much less subjected to secondary elaborations, such as over-compensation, displacement, symbolization and sublimation, than is the case in the typical obsessional neurosis. Those mechanisms tend to break down in the course of the depressions, and compulsions directed against external objects and the self appear undisguised and sometimes come precariously near to real action. The newly emerging obsessions are, as a rule, centred around the same complexes as are the habitual symptoms; e.g. a patient who had for many years been suffering from the compulsion to inspect the gas and water taps several times every evening lest his family may be drowned and gassed had periods of depression lasting for six months, during which the fear of having to murder his wife and child was the most prominent symptom. That compulsion had emerged only after the depression had been present for a week. It subsided completely with the depression. This is the type of case that is often diagnosed as recurrent or cyclical obsessional neurosis. In those cases the habitual obsessional symptoms which had been present for a long time prior to the depression are not always easy to ascertain during the depression, which is overshadowed by the much more spectacular recent obsessions.

* Read as a contribution to the symposium on "Psychodynamics of Depression" at the International Conference of Physicians in London on 10 September, 1947.

There is another feature which colours the depressive symptoms of the obsessional. It is the well-known tendency to doubt which makes the patient take up a critical attitude towards his ideas and even to his pathological mood. While the typical obsessional neurotic is preoccupied with the fear of doing wrong and with precautions against such impulses, and while the typical depressive patient is convinced that he has sinned, the obsessional going through a period of depression tortures himself with the fear that he may have done wrong in the past. The self-accusations often take the form of phobias projected into the past. They show a tendency to spread like obsessional ideas, and the patient would take obsessional precautions against them. An obsessional woman who, in her depressions, tortured herself with the fear that she might have done harm to a child many years ago, and accused herself of acts which she knew she had never committed, had worked out a ritual of avoiding children, with the professed purpose of not giving food to those self-accusations. Her attitude towards them was similar to that of the obsessional neurotic to his obsessions. In many of those cases the depressive mood does not dominate the clinical picture. Some psychiatrists are inclined to regard the depression in those cases as a natural reaction to an exacerbation of the obsessional illness. A variety of clinical facts which I pointed out some time ago (1) argue against such an explanation.

In studying those cases it becomes obvious that the obsessional personality structure has a modifying effect on the mechanisms of pathological depression. It tends to counteract regression to the deepest sadistic level, and to prevent a complete break with reality. Part of the aggressive impulses, which in the typical depression are mainly directed against the self, are diverted against external objects. Those impulses are subjected to the brake of obsessional ambivalence. Thus the obsessional personality structure exerts an integrating and preserving influence in a situation charged with enormous tension. We recognize the stabilizing effect of the obsessional personality structure which Glover (2) aptly called its buffer function. That effect can be demonstrated even more clearly in the interaction between obsessional and schizophrenic manifestations. Here we can study in action one of the " modifiers " postulated by Professor Kallmann (3) from the genetic point of view. Whether, in an individual case, such a modifying influence makes itself noticeable clinically must depend on quantitative factors.

If we take into consideration the two mechanisms which I have tried to demonstrate, namely the aggravating and unmasking effect of depression on overt and latent obsessional symptoms and the integrating influence of the obsessional personality structure on the depression, we shall, I think, arrive at a better understanding of some atypical clinical conditions often classed among borderline states. The majority of cases of so-called cyclical obsessional neurosis may become clearer and their spontaneous recoveries may appear less unexpected if we search closely for symptoms of depression and for a history of obsessional features.

The kind of interaction which I have just described is not the only one, but it is the most common. There are other forms of modification of depression by the obsessional neurosis and personality structure which I can only mention

briefly. There is one in which the habitual obsessions fade into the background during the course of the depression, which is characterized by marked aggressive behaviour, and another in which the depression becomes a masochistic orgy. In both those cases the symptoms are coloured by doubts.

In the few minutes at my disposal I could not give more than a rough sketch of some clinical observations which demonstrate the importance of the psychodynamic approach for symptomatology and diagnosis. These important aspects of clinical psychiatry will have to be cultivated again, if only to enable us to compare notes and to understand each other's language. It often seems that in our zeal for explaining and treating mental illness we are in danger of losing sight of what we are trying to explain and to cure.

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LUNG ABSCESS FOLLOWING ELECTRO-CONVULSIVE THERAPY: DESCRIPTION OF A CASE.

By Hugh Conway, B.Sc., M.B.Glasg., M.R.C.P.,
Assistant Physician to Out-patients, Western Infirmary, Glasgow.
AND
Humphry Osmond, M.R.C.S., L.R.C.P.,
Late Surgeon-Lieutenant, Royal Navy, Command Psychiatrist.

From the available literature it appears that inhalational abscess of the lung following E.C.T. is a rare condition, but it is difficult to assess the actual incidence. Cook (1944), in his extensive review of the subject, quotes Meduna and Friedmann (1939) as stating that lung abscess occurred in 0·1 per cent. of cases, but this probably refers to patients undergoing metrazol convulsions, in whom there is an additional risk of embolic abscesses due to mobilization of thrombus at the site of injection. Jessner and Ryan (1943) mention that aspiration pneumonia may complicate metrazol treatment, and that pulmonary abscess may occur as a result of old pelvic thrombo-phlebitis or from mobilization of thrombus at the site of injection. They do not refer to inhalational lung abscess complicating E.C.T. Sargant and Slater (1944) state that chest complications are rare after convulsion treatment. Kraines (1943) and Brain and Strauss (1945) do not discuss the condition. Vassallo (1946) in an unpublished series of over 300 cases has observed one inhalational lung abscess. Kalinowsky and Hoch (1946) say: "The development of pulmonary diseases during treatment is rare in E.C.T., but was quite frequent in metrazol therapy." They mention some possible reasons for this, e.g. abscess due to mobilization of thrombi at the site of injection. They add: "The literature on E.C.T. contains only one case of pulmonary abscess" (Kalinowsky and Werthing, 1943). The paper quoted, however, merely states, that the patient developed a lung abscess which was successfully treated with sulphanilamide. All authorities agree that pre-existing lung disease, and especially tuberculosis, is a strong contra-indication for E.C.T. Since there are so few references to this illness in the literature it seems profitable to describe a case.

Case history.—Maltese, male, driver R.A.S.C., aged 32 years.

Admitted to a General Hospital in Malta on 8 February, 1946, as a transfer from a hospital in the Middle East, where a diagnosis of psychopathic personality had been made. Previously, in May, 1944, and January, 1945, there had been two brief psychotic episodes in which he had been violent, aggressive and hallucinated.

Apart from a history of fits in childhood there was nothing of note in the previous history. His father and a paternal uncle were also reputed to have had fits.

He joined the Army in 1940; there was no evidence that he had undergone battle stress.

Before admission he refused food for three days and required rectal feeding.

On admission he refused to speak, would not feed himself and was completely indifferent to his surroundings. A provisional diagnosis of catatonic schizophrenia

was made and it was decided to treat him by E.C.T. Physical examination was negative except for his mouth, which was foul. Captain E. M. Davison, A.D.C., diagnosed Vincent's infection ; the teeth were sound. Treatment with potassium bichromate and hydrogen peroxide was instituted ; there was rapid improvement. On 12 February, 1946, a chest X-ray was negative. On 16 February his mouth was clear and on the following day the first convulsion was given, using a McPhail-Strauss Universal Electroplexy apparatus : subsequently, four more were given on 19, 24, 26 February and 5 March. None of these was particularly violent or in any way abnormal ; the voltage used was 80 with a current of 100 milliamps. lasting ·35 of a second. The duration of the fits was never more than 40 seconds. From the beginning of treatment he showed a marked change for the better; he was approachable, co-operative, fed himself and was up and about in the ward.

On 8 March, 1946, he first complained of cough, associated with purulent sputum, which was not foul smelling, and pain in the front of the chest ; the evening temperature was 101° F., but there was no rigor. These symptoms persisted and fever continued for 5 days, varying from 100° F. to 102° F., and then fell by lysis. On 13 March the temperature was 99° F., and apart from scattered rhonchi there was nothing obvious on physical examination. A provisional diagnosis of virus pneumonia was made. A chest X-ray on 14 March showed infiltration of the whole of the left upper and mid zones, and a large thin-walled cavity with a fluid level in the left infra-clavicular region. The radiologist thought that this picture suggested pulmonary tuberculosis, but in view of the history and the recent negative X-ray lung abscess seemed more probable. Facilities for bronchoscopy were not available. Six sputum examinations were made ; they were purulent, but contained no blood, and no tubercle bacilli were found ; the organisms were staphylococci, streptococci and pneumococci, with none predominating. All were penicillin-sensitive. The leucocyte count was 19,500 per c.mm. (polymorphs 90 per cent.). On 22 March postural drainage and penicillin treatment (25,000 units 3-hourly) was begun. There was a gradual but definite improvement in his condition ; the postural drainage was very successful and the temperature remained normal. Despite knowledge of the site of the abscess there were never any physical signs. An X-ray on 6 April showed that the cavity was much smaller and that the surrounding consolidation was resolving. X-ray of the sinuses was negative. He remained afebrile and by 15 April his general condition was good, and, since he was producing no more sputum, postural drainage was stopped and he was allowed up. The chest was re-X-rayed on 16 April and there was further improvement. Although his dental hygiene remained poor there was no specific lesion. On 27 April his general condition was good, his weight was increasing, his appetite was improved and he had no cough, but an X-ray showed some deterioration—the cavity was multilocular, and there was a fresh area of consolidation medial to it. The leucocyte count was 17,900 per c.mm. He remained ambulant, mobile and symptomless, and from a further X-ray on 5 May it was clear that there was considerable improvement and that the consolidation had disappeared. The leucocyte count was 8,000 per cu. mm., with a normal differential picture, and the penicillin, which had been given all this time, was stopped—the total was 8,255,000 units.

He was still passive and unresponsive and took little or no interest in his surroundings ; for hours on end he sat or stood in one position, but if encouraged would walk about and carry on a desultory conversation. Shortly afterwards he was transferred to the Civilian Mental Hospital, when his physical condition was good and his mental condition showed no further improvement.

Discussion.

This case demonstrates one of the little-emphasized dangers of E.C.T., and illustrates some of the difficulties which can arise. In the available but representative literature at our disposal, only Cook (1944) stresses the need for thorough preliminary dental examination, and the potential dangers of oral infection or other dental disease. This patient was known to have a gum infection and full precautions were taken, but even so he developed a lung

abscess, which was presumed, despite its site, to be inhalational, because there was no evidence of any nidus from which an embolus could have arisen.

All authorities agree about the danger of lighting up a latent tuberculous infection by E.C.T., but the possibility that this patient's lesion was tuberculous was excluded by the negative chest X-ray before treatment began, by the absence of tubercle bacilli in the sputum, and by the response to treatment. The first X-ray following E.C.T. strongly suggested tuberculous infiltration with cavitation, and, but for the fact that a previous plate had been taken, treatment might have been dangerously delayed—the more so because of the slight degree of systemic upset. The leucocyte count was a valuable guide.

This complication affects the prognosis in a peculiar way. Owing to the necessary abandonment of the sequence of E.C.T. the patient did not maintain his initial improvement, and his mental condition worsened gradually. Because of his reduced activity, apathy and immobility the recovery of his lung condition may be transitory and the final prognosis doubtful. It is unhappily clear that a vicious circle has been established; and it is difficult to see how this can be broken except by a spontaneous remission, since neither E.C.T. nor insulin therapy can now be given.

Because of the inherent dangers it has long been recognized by psychiatrists that a chest X-ray is required before treatment is begun, but of five well-known authorities only Cook (1944) emphasizes that a full dental examination is essential. These precautions will have to be observed with even greater care, since E.C.T. is becoming a feature of out-patient psychiatry.

In dealing with patients who have had E.C.T., the physician must not ignore what may appear to be minor complaints, since a serious organic lesion may be present in an unco-operative or apathetic individual, with few physical signs and little systemic disturbance. There is always the temptation to ascribe minor aches and pains to the effects of treatment or mild intercurrent infection, but, when there is any doubt, a second chest X-ray is always justified.

Summary.

A case is described in which an inhalational, non-putrid lung abscess developed in a patient with schizophrenia treated by E.C.T. Some suggestions are made about precautions which should be taken both to prevent and diagnose this complication.

Addendum.

On 4 September, 1946, after this paper was completed, we saw the patient again at the Hospital for Mental Diseases, Malta. His physical and mental condition had deteriorated. There was a low grade fever, B.S.R. was 37 mm. in one hour, leucocyte count was 14,000 per c.mm., and chest X-ray suggested a recurrence of the abscess. He was completely withdrawn and negativistic. His general nutrition, which was good, was being maintained by tube feeding.

We wish to thank Colonel W. D. Anderton, M.C., D.D.M.S., Malta Command, and Colonel F. Holmes, O.B.E., Officer Commanding, 90 Military Hospital,

for permission to publish this case ; also Professor V. Vassallo, O.B.E., Director of the Hospital for Mental Diseases, Malta, for allowing us to see the patient while under his care, and for the kindly interest he has shown.

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Part II.—Reviews.

Chemistry of Muscular Contraction. By A. Szent-Gyorgyi. New York: Academic Press Inc., 1947. Price 25*s*.

This book, amplifying the Cameron Prize Lecture of 1946, describes the modern conception of muscular contraction and shows the steps by which these advances were made. It is a stimulating account written by one who has contributed much in this field.

It is a fascinating story. Two of the proteins of muscle, myosin and actin, have been shown to be capable of existing in two forms—either fibrous and extended or globular and coiled. They readily form a compound, actomyosin, in which the two types of molecules are each in the extended form and are combined side by side so as to make a double fibre. In certain ionic and enzymatic conditions the extended fibrous molecules shrink to the globular and coiled form, but the myosin on one side of the fibre shrinks more than the actin on the other side, so that the whole long fibre coils up like a spring. The principle is similar to that of the "bimetal" strip except that the changes are chemical instead of thermal.

Such a contraction needs energy. It is now known that the extended "relaxed" actomyosin molecule contains the necessary free energy for contraction in its molecular bonds, the free energy available ($-\Delta F$) being about 7,000 calories. This energy is immediately available, and needs only a suitable change in the ionic conditions for its release. Relaxation, i.e. the return from the coiled to the extended form, cannot occur unless fresh energy is supplied. For some time it has been known that this is obtained by the dephosphorylation of adenosine triphosphate (ATP), and it has also been known that myosin is itself an enzyme for this reaction, but the full method has been found to be unusually simple and automatic: myosin catalyses the dephosphorylation of ATP, thus obtaining by direct contact the energy of the energy-rich phosphate bond, but it has this property when it is in the contracted coiled form only! The result is a simple and stable dynamic system: when in the coiled form, myosin dephosphorylates ATP and obtains the energy required for extension, but when extended it has no action on the ATP. In this way a constant waste of energy is avoided, while energy is immediately available when required.

The story, in addition, has many interesting suggestions that these processes are not entirely unrelated to the processes of neuronic action. (These fundamental biochemical processes in tissues are often related because it is quicker, in evolution, to improve or modify an existing process than to wait for a chance mutation evoking something quite new.) Be that as it may, the reader cannot help noting in this account the repeated references to matters well known to be of importance in the biochemistry of the neuron. Thus, myosin and actin are both highly sensitive to potassium, and form with this element compounds containing it in large quantity, their own properties being markedly altered by the combination. These effects of potassium are often markedly opposed by calcium. When myosin and actin combine, potassium is released in large quantities into the surrounding fluid, and this increase in concentration of ionic potassium in the fluid promptly affects in its turn the properties of the actomyosin just formed. So the process tends to be autocatalytic, only a small disturbance being required to initiate the whole process. "These details may have physiological importance, and suggest that ionic balances

cannot be looked upon as static environmental factors permanently conditioning certain kinetics. Their slight changes might have trigger actions, or might be the safety buttons which block the trigger."

A stimulating book which can be recommended. W. R. ASHBY.

Clinical Studies in Psychopathology. By HENRY V. DICKS, M.D., F.R.C.P. London: Edward Arnold & Co., 1947. Second edition. Pp. 238. Price 15*s*.

Dr. Dicks' broad approach to psychological problems is well illustrated in this excellent book, now in its second edition. There are chapters on anxiety and obsessional states, hysteria, sexual perversions and abnormalities and drug addictions. There are only minor alterations in the new edition, except in the last chapter.

If Dr. Dicks is broad-minded and tolerant towards the diverse views of the various psycho-pathological schools, the same cannot be said for his attitude towards those who approach these problems from the physical and constitutional side. These are accused of trying to reduce "desire, zest, truth, love, knowledge and values" to Pavlov's reflexes. Slater, in particular, is criticized because of the importance he assigns to organic damage and the primacy of constitution, "and moreover constitution regarded as an unalterable, structural, static matrix, on which events act mechanically as 'conditioning' forces, *a la* Pavlov." Again, he complains that Slater slurs over a great mass of psychoanalytical experience with these few words: "Psychological and physiological conditioning produced by the environmental circumstances of the past."

The reviewer finds it very hard to believe that Slater could have described a living and growing organism as passive and unalterable. If, however, it is allowed that behaviour is the inevitable result of environmental and constitutional forces, surely there is room for all the mechanisms of Freud, the psychotherapeutic activities of Dr. Dicks and the physiotherapy of Dr. Slater.

Dr. Slater is also condemned for trying to explain the music of a violin by the effect of the horse-hair scraping on a cat's entrails, and there are several variations on this metaphor. However, if a wireless set transmits an inadequate performance of Bach's Chaconne, the first reaction is that the soloist is constitutionally incapable of rendering Bach, and that is usually the correct answer. Of course other factors should be excluded, such as the violin itself, the acoustics of the hall, the transmitting and receiving sets, and the experience of the listener should be checked against that of experts. Finally it is possible that the executant had been badly trained. If such were the case an intensive course of re-conditioning by a Doctor of Music might be worth considering. One things seems impossible to get to grips with or explain and that is the aesthetic experience itself. STANLEY M. COLEMAN.

Old Age: Its Compensations and Rewards. By A. L. VISCHAR, M.D. London: George Allen & Unwin, Ltd., 1947. Pp. 200. Price not stated.

Having spent over twenty years in charge of "The Old People's Home" at Basle, the author is entitled to speak with authority on this subject. Dr. Vischar's book makes delightful as well as interesting reading, and there is a wealth of quotation, both scientific and literary. The book will probably leave the reader with the feeling that though much thought and research has been undertaken by many workers, our knowledge of the problems of old age are extremely meagre. We do not know the cause of ageing, though there have been interesting theories by Metschnikoff, Carrel, Bustai and others. We cannot clearly differentiate between normal senescence and pathological processes. We do not know what factors are responsible for longevity, and there

has been little success with experiments in rejuvenation and the prolongation of life.

Though the words of the Preacher are quoted, as also the pessimistic description by Grukle, it appears that the author holds a more optimistic outlook, and he quotes as well as says much of an opposite opinion. Regarding the achievements of old age, the author is interested in Brinchmann's examination of the creative works of aged artists. Brinchmann found that with age the artist passes from a dynamic phase in middle life to one of increasing introversion. The book contains a number of plates to illustrate this theory.

STANLEY M. COLEMAN.

Foundations of Dreams Interpretation. By SAMUEL LOWY, M.D. London : Kegan Paul, Trench, Trübner & Co., Ltd., 1946. Reprinted. Pp. xiv + 260. Price not stated.

The author, a pupil of Stekel, employs the active and intuitive method of dream interpretation. His approach to the subject is a psycho-biological one, and it is held as a fundamental that the dream is a representation of the whole ego, as a psycho-somatic unit. He believes that the conceptions of Freud, Adler, Jung and Stekel are by no means in true contrast to each other ; rather they are complimentary.

It is the thesis of this book that the importance of somatic stimuli in dream formation has been neglected in favour of psychic causation. It is held that there is a need for a unified conception of the total dreaming process, which would consider the two kinds of dream stimuli as having a common denominanator. The manifest dream as a conceptionalized and verbalized event arises at the subconscious level. Below this are the deep dream processes, the real source of the manifest dream. These are non-conceptional, affect-energetic events, arising at a level where psyche meets soma. It is believed that the normal functioning organ bombards the brain with stimuli, interpreted by the psyche as affect, and that this is the normal contribution of the organ to the dream formation. The overstimulated organ, physiologically or pathologically, produces an overdose of affect and the simultaneous stirring up of associated complexes. Dream formations are cited as being determined by peristalsis of the overloaded stomach, bronchitis impeding the breath, toothache, fever, the urinary urge, erection and pollution, etc. These vegetative sources are just as important as psychical stimuli to the dream formation.

Unlike the Freudians, dream gaps, dream distortion and dream symbolism are held to be due to the inability to conceptionalize or verbalize many of the deep-dream processes, which are either unthinkable or can only be represented symbolically.

It has to be said that the author's style does not make for easy reading. Again, while there is much repetition, conclusions and opinions are not clearly summarized. It is, however, an important contribution to the study of dreams in particular, and to the theory of the unconscious in general.

STANLEY M. COLEMAN.

Psychiatric Research. Harvard University Press (London : Geoffrey Cumberlege), 1947. Pp. 113. Price 11*s.* 6*d.*

This is No. 9 of the Harvard University Monographs in Medicine and Public Health, and consists of papers read at the Dedication of the Laboratory for Biochemical Research, McLean Hospital, Waverley, Mass.

The six chapters are devoted to research at the McLean Hospital, biochemical problems related to psychiatry, the integration of medical and psychiatric problems, protocol for a review of psychiatry, psychical seizures, and the psychobiology of psychiatric research.

The best chapter in the book deals with the biochemical problems related to psychiatry, by Jordi Folch. He draws attention to a number of facts

which are not well enough recognized—that the brain uses one-fourth of all the oxygen consumed by the body under basal conditions; the metabolism of the brain is highly specialized—for instance it does not require insulin to use glucose—and the pituitary diabetogenic hormone plays no part in its carbohydrate metabolism. The brain lipids are never used as a source of energy; if a dog is starved to death, its brain weighs just as much as a litter-mate that has been well fed and then killed at the same time. Myelinization of the central nervous system also is not affected by starvation.

The chapter on the integration of medicine and psychiatry is a most interesting study in psychosomatic medicine, with neurocirculatory asthenia as the syndrome chosen for investigation.

Altogether a stimulating and worth-while contribution to psychiatry.

G. W. T. H. FLEMING.

Current Therapies of Personality Disorders. By BERNARD GLUECK, M.D. London: William Heinemann, 1946. Pp. 296. Price 17*s.* 6*d.*

This volume contains the proceedings of the Thirty-fourth Annual Meeting of the American Psychopathological Association, and is edited by Bernard Glueck, who delivered the presidential address, "Psychiatry: an Instrument of Personal and Social Rehabilitation."

The book is divided into four sections, the first dealing with the modern psychiatric hospital, the second with physico-chemical techniques in psychiatry, the third with psychotherapeutic techniques in psychiatry, and the fourth with psychiatric guidance and rehabilitation techniques.

In dealing with electric-shock treatment we think it wrong to talk about "complete lack of any discomfort on the part of the patient and therefore his perfect co-operation." There may be a difference between American technique and mentality, but it is certain that there is a considerable degree of objection by the patient in this country to electric-shock treatment. The use of curare is deprecated. The writer very wisely emphasizes special management during E.C.T. and for three weeks following. There appears to be too much of a tendency to treat E.C.T. in a carefree manner as an out-patient treatment without any "post-operative" treatment. If possible, hospitalization during and for three weeks afterwards should always be aimed at as a very sound practice.

The chapter dealing with the conditioned reflex treatment for alcoholics is well done and well worth reading. G. W. T. H. FLEMING.

The Physical Background of Perception. By E. D. ADRIAN, O.M., F.R.S. Oxford: Geoffrey Cumberlege at the University Press, 1947. Pp. 95. Price 10*s.*

The Wayneflete Lectures for 1946 delivered in the Hall of Magdalen College were devoted by Prof. Adrian to the path of perception from sense-organ to the grey matter of the brain responsible for sorting out the responses to stimuli.

The book is divided into six chapters devoted to the brain and the mind, the sense-organs, motor and sensory areas of the brain, sight and hearing, the electrical activity of the brain and recognition and mental events.

The best chapter in the book is that devoted to the electrical activity of the brain, where the author gives us a good account of the α rhythm and its development. G. W. T. H. FLEMING.

Suicide and the Meaning of Life. By M. VON ANDICO. London: William Hodge & Co., 1947. Pp. xv + 219. Price 8*s.* 6*d.*

This small book is a study of attempted suicide amongst individuals sent by the police commissioners in various districts in Vienna. The author makes the assumption that because 100 cases of hers have attempted suicide, they

had come to feel that life was meaningless. Most of her statistics are valueless, as they are not compared with comparative age-groups of the non-suicidal population. When *will* writers learn to present control material so that their *results* may have *some* meaning, as well as life. G. W. T. H. Fleming.

The Psychology of Behavior Disorders. By N. Cameron, M.D. Boston: Houghton Mifflin Co., 1947. Pp. 622. Price $5.

This book is written by a psychiatrist with a Ph.D. in psychology. A considerable proportion of the book is devoted to the psychoneuroses, which is very much in its favour.

The author's outlook is primarily a biosocial one, which is quite different from the prevailing psychosomatic approach and is more in line with the teaching of Adolf Meyer.

When *will* someone write about the psychopathology of the completely normal adult (if such exist!)? How many of these normal and healthy people can also say, "My mother never expected to raise me"?

There is far too much tendency in modern psychology to assume that because a child fell on the back of its head it must blame all subsequent aberrations of conduct on this—but have not 100 per cent. of children fallen on the back of their heads, been shut in dark cupboards, been frightened by a furry animal?

The author rather tends to pooh-pooh the fatigue syndrome, effort syndrome or what others call neuro-circulatory asthenia.

In a more advanced degree how familiar the experienced psychiatrist is with blue hands and feet, and if he has had an adequate pathological training, with small hearts and small aortas.

Neurocirculatory asthenia is a very real constitutional condition, and is therefore not an easy condition to treat.

Will medical writers ever cease using the expression autoerotism when they mean masturbation?

These, however, are small blemishes in a book which is very readable and very much worth reading. G. W. T. H. Fleming.

Practical Psychiatry and Mental Hygiene. By S. W. Hartwell, M.D. New York and London: McGraw-Hill Book Co., Inc., 1947. Pp. 439. Price $3.75.

This volume in the McGraw-Hill series in nursing is written, so the author states, "to help the student develop a dynamic interest in psychiatry, to make psychiatry more easily understood, to make the teaching of psychiatry practical and to permit flexible use of the text."

The book is arranged in four parts, the first dealing with psychiatry as a whole, the second with the basic medical sciences and with psychology, the third with descriptive psychiatry, and the fourth with the mental hygiene of children and adults.

The bibliography is rather too extensive and technical for most of those who will read this book.

The book is very well done and pleasant to read, and would prove a great boon to many medical men. G. W. T. H. Fleming.

A Text-book of Mental Deficiency (Amentia). By A. F. Tredgold, M.D., F.R.C.P. Seventh edition. London: Baillière, Tindall & Cox, 1947. Pp. 534, with 47 plates. Price 30*s*.

It is not necessary to say much in praise of this well-known text-book. It is the best book on mental deficiency in the English language. The writer has added a considerable amount of new matter, but might have added a lot

more on present-day mental testing, together with the changes arising from the Education Act, 1944.

At the same time one does wish that the term amentia could be dispensed with and the term oligophrenia used instead. The word amenza in Italian means confusional insanity, and is so used, and in Holland also amentia is regarded as confusional insanity. G. W. T. H. Fleming.

The Neocortex of Macaca Mulatta. By G. von Bonin and P. Bailey. Illinois: The University of Illinois Press, 1947. Pp. 163 and 62 plates. Price 20*s*.

This is one of the volumes of the Illinois monographs in the Medical Sciences based on microscopical work done in the Department of Neurology and Neurological Surgery of the University of Illinois.

The macaque cortex lends itself to a more natural subdivision into functional areas than the human cortex. The occipital cortex is concerned primarily with vision, the parietal with somaesthetic and acoustic sensations, and the frontal cortex may also be a functional unit. The human cortex is, of course, a more elaborate affair. There does, however, appear to be a common primate pattern, but much more work must be done on the primate cortex before any conclusions can be drawn.

The body of the book is largely a description of the plates, which are very well reproduced.

There is an excellent bibliography.

The book, although entirely one for the research worker and specialist, is well worth reading by those whose comparative neuroanatomy is equal to it!

G. W. T. H. Fleming.

Diseases of the Nervous System. By W. Russell Brain. Geoffrey Cumberlege at the Oxford University Press, 1947. Pp. 987 + xviii, with 79 figures. Price 37*s*. 6*d*.

The third edition of this most excellent text-book of neurology needs little introduction. The first two editions were extremely well done, and this one lives up to the standard set.

The most striking addition is the chapter on nutritional disorders of the nervous system. Here we think some mention of sub-clinical pellagrous states might have been included. These are not uncommon in this country, and are not confined to the inmates of mental hospitals. There is also added a section on the status of psychogenic symptoms and psychotherapy, and another on psychometric tests. This latter section is rather scrappy; it is a very wide subject, and if it is going to be dealt with should be dealt with at greater length—probably much greater length than is suitable for a text-book of neurology.

The author describes the use of penicillin in the treatment of neurosyphillis and of meningitis. Illustrations of typical electroencephalograms have been added.

The book has been improved, and possibly the greatest compliment one can pay the author is to say that it resembles even more closely than the previous edition, Kinnier Wilson's monumental classic.

G. W. T. H. Fleming.

Neurology. By Knud H. Krabbe, M.D. London: Humphrey Milford, Oxford University Press, 1941. Price

This book, which was published as long ago as 1941, consists of lectures given by the writer to his students in Copenhagen during the last 23 years, and is intended primarily for students and general practitioners.

There is a sound account of the methods of clinical examination of the nervous system, and all through the book the author quotes his own experience.

A most readable book, and one which will be read with benefit as a supplement to most text-books and giving the Danish point of view.

G. W. T. H. Fleming.

Studies on the Morphogenesis of the Brain in Reptiles. By Knud H. Krabbe. Copenhagen: Einar Munksgaard, 1939. Pp. 87, with xxiii plates.

Studies on the Morphogenesis of the Brain in Lower Mammals. By Knud H. Krabbe. Copenhagen: Einar Munksgaard, 1942. Pp. 124, with xxxi plates.

Studies on the Morphogenesis of the Brain in Hydracoidea, Ungulata, Carnivora and Pinnipedia. By Knud H. Krabbe. Copenhagen: Einar Munksgaard, 1947. Pp. 107, with xxx plates. Price 35 Dan. Cr.

These three beautifully produced books are from the Tornblad Institute for Comparative Embryology at Lund, Sweden.

In the first volume the author chose an example from each of the five orders of reptiles, and tried to obtain stages from each corresponding as near as was possible. When the diencephalon occupies a large volume and the mesencephalon is not yet divided into its two hemispheres the brains begin to develop in very different directions. The possible common ancestors of the reptiles go far back; differentiation between the various orders began at a comparatively early stage. The early divergence of the brain of the chameleon from other reptile brains shows that it is comparatively far removed from other Saurians.

In the second volume it is pointed out that the brains of the lower mammals resemble those of the Saurians. However, the hypothalamus occupies more space. The cerebral development of Echidna sets it apart from other lower mammals, but it is more closely related to them than to the Saurians.

In the third volume the author includes a description of a lion embryo of 5 mm.—surely a *very* rare possession; seals are an unusual group. The concluding chapter on the general development of the brain is very well done.

The illustrations in both books are very fine, and a very good indication of the standard set in work of this type from the Scandinavian countries.

G. W. T. H. Fleming.

The Practice of Mental Nursing. By May Houliston. E. & S. Livingstone, Ltd.

This little book condenses into 158 pages a very wide range of practical advice to the beginner in mental nursing. Miss Houliston, formerly Senior Sister Tutor and now Matron of the Crichton Royal Hospital, comments in her preface on the fact that the curriculum provided for the first-year nurse offers no instruction on the everyday psychiatric problems met with in the wards. Her book is intended to fill this gap, and to supplement the rather academic early period of training.

The author preserves a colloquial style which makes for effortless reading, and the use is avoided of all but the most essential technical terms. Almost every page is devoted to purely practical matters, and even the preliminary historical survey of psychiatric development says no more than is necessary to giving the student an understanding of the scientific, as distinct from the emotional attitude towards mental disorder.

The main points are summarized at the end of each chapter. The student will not be disheartened on reading the rather formidable list of qualities considered to be desirable attributes of a good nurse, for Miss Houliston clearly

follows St. Paul in believing that charity is the foundation of all other virtues, and she emphasizes that good nurses are made, not born.

The chapter on normal psychology is concise, and the author's teaching experience is revealed by her use of diagrammatic illustrations, and their subsequent transposition into the field of practical issues. However, the impossible task is attempted of describing the basic features of dynamic psychology in a matter of three pages, and the degree of dogmatism essential to good teaching is, at this point, overstretched.

Only the more important psychoses and neuroses are briefly described, as befits a work of this kind, but their accompanying disorders of behaviour and the appropriate nursing attitudes and actions respecting them are excellently portrayed. Attention is given to the various ways in which a nurse may give the newly-admitted patient that all-important good first impression of the hospital, and a chapter is devoted to matters and problems particularly affecting nurses on night duty. Any nurse who commits to memory the wealth of practical advice given should find herself never at a loss in dealing with any of the usual daily problems.

Occupational therapy is given the prominence it deserves, and the ways in which the nurse, as well as the occupational therapist, play a part in furthering this essential form of treatment are dealt with admirably.

The final chapter briefly describes the functions of a psychiatric social worker. It fails to harmonize with the main subject matter, and could be omitted without detriment to the work as a whole.

The book represents an ample achievement of the author's purpose, and should prove to be a very acceptable and useful standard issue in any preliminary training schools for mental nurses. OTHO FITZGERALD.

Part III.—Bibliography and Epitome.*

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Localization of Intracranial Tumors by Electroencephalography.

In a series of 60 verified intracranial tumors electroencephalography indicated the affected hemisphere (unipolar leads) in 72 per cent., while 10 per cent. were wrongly localized and 18 per cent. could not be localized as to hemisphere. With bipolar leads phase reversal was found corresponding to the tumor in 51 per cent., while low frequency potentials were found over the tumor in 73 per cent.

(Authors' abstr.)

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* A number of extracts in this section are reproduced from *Chemical Abstracts* and *Psychological Abstracts*. To the Editors of these two Journals we extend our grateful thanks.

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Tridione Therapy.

1. A progress report of clinical observations in the therapeutic use of tridione on 136 cases of varied neurological manifestations, over a period of 2 years, is presented.

2. As previously reported, most spectacular benefits were obtained in cases of *petit mal*, where clinical improvement was immediate, associated with improvement in the EEG pattern, and sustained often after cessation of the drug.

3. Tridione appears to be useful as an adjuvant drug in the treatment of *grand mal* seizures, though it does seem to aggravate some cases.

4. Both *grand* and *petit mal* of the idiopathic type were more responsive than those due to organic lesions.

5. Anticonvulsant action is indicated by its beneficial effects in cases of tetanus.

6. Tridione is of value in cerebral palsy, especially for reducing tension of the athetoid type.

7. Some forms of behavior disturbances are sedated by tridione.

8. Site of action for tridione appears to be the mid-brain and (with some selectivity) the basal nuclei, an inference drawn from its failure to help patients with pyramidal lesions, while markedly benefiting extra-pyramidal lesions, with the exception of chorea, parkinsonism, and dystonia.

9. Toxic side-effects in the use of tridione, in the author's experience, were rare in children, were generally innocuous, and seemed readily reversible with cessation of the drug. More severe reactions were seen in adults.

(Author's abstr.)

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Report on Lobotomy Studies at the Boston Psychopathic Hospital.

It is clear that the results of prefontal lobotomy are quite variable. Clinically a few cases are dramatically improved and may be restored to a healthy efficient life in the community, a rather large number are partially improved or rendered more comfortable, and a good many are essentially unchanged. There is always a small but definite risk to life, and there is always the possibility of producing new and undesirable symptoms. As yet, we are quite unclear as to the exact indications for the operation. However, we would venture the opinion that by selection of early and relatively well-integrated cases we would get a better percentage result. We would go on record as saying: that lobotomy is a good method, perhaps the foremost method, for the treatment of the chronic mentally ill patient.

The changes in the personality are very variable and complicated and great caution should be exercised in interpreting psychological results. There is no question that prefontal lobotomy offers a very rich field for research.

(Authors' abstr.)

The Significance of Alpha Variants in the EEG, and their relationship to an Epileptiform Syndrome.

1. Evidence has been presented to show that the cerebral psychomoter patterns of Gibbs, Gibbs and Lennox are related to certain variations of the 10-cycle or alpha rhythm of the brain, which have been termed alpha variants. The most common variants consist of a halving or doubling of the alpha rate.

2. Even in cases of known psychomotor epilepsy the amount of the alpha variants recorded in the EEG between attacks may vary widely both among and within individuals, but practically all such patients show traces of the variants between seizures.

3. There is a high incidence of alpha variants in certain other conditions, notably psychoneurosis and idiopathic epilepsy. Their presence in the so-called psychoneurotic group shows a high correlation with a symptom complex that includes cranialgia, episodic changes in levels of consciousness, and emotional and vasomotor disturbances.

4. A high incidence of alpha variants among patients with *grand mal* epilepsy has been noted. The alpha variants may be correlated in these cases with altered states of consciousness (which cannot be identified electroencephalographically with *petit mal*), or with neurotic traits superimposed on the major epilepsy. It is concluded that mixed epilepsy of a *grand mal*-psychic variant type is of frequent occurrence.

5. The alpha variants are not pathognomonic of the epileptiform states. The significance of their appearance in the EEG without the accompanying symptom complex, as in the case of a small proportion of presumably normal individuals, has not yet been elucidated.

6. The alpha variants are of diagnostic assistance in cases where the neurological findings are essentially negative, and where the EEG is otherwise within broad normal limits. Under these circumstances, their presence in the EEGs of patients with vasomotor instability (cranialgia, dizziness, etc.), emotional disturbance of an episodic nature, or changes in the state of consciousness, indicate that the condition may be related to an epileptiform syndrome, rather than to a purely psychosomatic etiology.

7. The term psychomotor epilepsy is inadequate to describe the entire range of psychic variants in the epileptiform syndrome, and in the author's opinion should either be replaced by a more descriptive term, or its use restricted to conditions in which motor manifestations of a bizarre nature are present. (Author's abstr.)

EEG Studies in Idiopathic Epilepsy, Idiopathic Syncope and Related Disorders.

The physiological and psychological factors relating to idiopathic syncopal attacks are discussed since this symptom was predominant in the group discharged with non-epileptic diagnoses.

The symptoms produced by arresting cerebral circulation in man and the syncopal attacks observed in certain cases of personality disorder and psychoneurosis are compared.

The ultimate discharge diagnosis and EEG correlation were considered in 469 patients admitted with a diagnosis of epilepsy or a possible convulsive disorder, and analysis showed that less that half were discharged from the naval service with a diagnosis of epilepsy and that the EEG abnormalities were significantly higher in this Group.

Of 469 cases admitted with the possibility of a convulsive disorder 147 were discharged with a diagnosis of personality disorder and 62 with the diagnosis of psychoneurosis which made up about 44 per cent. of the admission group.

Analysis of 206 cases discharged from a U.S. Naval Hospital with a diagnosis of epilepsy is presented. The EEG findings are compared with a control group. There is a similarity between Gibb's series of EEG findings in 730 adult epileptics and with his series of "controls."

Nineteen cases or 9·6 per cent. of the series gave a history of head injury 1–10 years prior to their first convulsive seizure.

Of these 19 cases, 11 had abnormal EEG, 5 of which were focal in type.

Of this series 127 patients had been observed in typical *grand mal* seizures and of this group 63 per cent. had greatly abnormal EEG and 11·8 per cent. showed slightly abnormal EEGs.

Typical *petit mal* histories in this series were rare as were typical *petit mal* waves in the EEG tracings. A possible explanation for this may be that all of the patients considered were over 17 years of age and 90 per cent. of them were in the age group of 17–30 years and the remaining 10 per cent. were over 30 years of age. (Author's abstr.).

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Activated Electroencephalography.

In a series of 97 patients with post-traumatic epilepsy, an attempt was made to activate the epileptogenic focus by hyperventilation, hydration, electric shock, intravenous administration of alcohol, and injection of trimethadione, penicillin, acetylcholine chloride, sodium cyanide and metrazol.

Of these methods, the injection of metrazol proved to give satisfactory focal activation in approximately 44 per cent. of the patients on the first test and in a much higher percentage on repeated testing.

Intravenous administration was more effective than intramuscular injections.

Clinical seizures occurred in approximately 14 per cent. of patients, but not if anticonvulsant medication was given before the test.

The electroencephalographic alterations induced with metrazol included focal slow waves, spikes or, somewhat less frequently, the rhythmic discharge of a seizure. The same alterations were less commonly recorded from all parts of the head.

Activated electroencephalography appears to be a useful diagnostic aid in the understanding of the mechanisms involved in post-traumatic epilepsy.

(Authors' abstr.)

Relation of the Frontal Lobe to the Autonomic Nervous System in Man.

The autonomic nervous system was examined in a control group and in a series of patients who had undergone prefrontal lobotomy. The sympathetic nervous system was tested pharmacologically with intravenous injection of 0·05 mgm. of

epinephrine hydrochloride (1:1,000). The parasympathetic system was examined by means of stimulation of the carotid sinus reflex. The effects were recorded with the electrocardiograph and the electroencephalograph, and the clinical manifestations were carefully noted.

Subcortical section of the frontal lobes interferes with inhibitory and excitatory autonomic centers in the cortex, resulting in overreaction of the autonomic nervous system to direct stimulation.

After frontal lobotomy autonomic equilibrium is eventually established at a new level and is brought about by readjustments of the autonomic system.

This work confirms other reports that cortical representations of the autonomic nervous system are located in the prefrontal area. (Authors' abstr.)

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Ballism and the Subthalamic Nucleus (Nucleus Hypothalamicus; Corpus Luysi): Review of the Literature and Study of Thirty Cases.

A review of the literature disclosed 30 cases of hemiballism associated with localized pathologic change in the subthalamic nucleus. Analysis of these cases led to the following conclusions:

1. Ballism is a distinct form of involuntary movement characterized by continuous, violent, coordinated activity of the axial and proximal appendicular musculature such that the limbs are flung about.

2. Hemiballism, and sometimes monoballism of the upper extremity, is the apparently inevitable symptom in man of destruction localized in the contralateral subthalamic nucleus (nucleus-hypothalamicus; corpus Luysi).

3. There is evidence that interruption of the connections of the subthalamic nucleus may result in hemiballism.

4. Hemiballism may appear without demonstrable pathologic change in the subthalamic nucleus or its connections, although such cases are relatively rare.

5. Ballistic movements may appear in a variety of dyskinesias, to which the relation of the subthalamic nucleus is as yet obscure. Their similarity to or identity with those of hemiballism following damage to the subthalamic nucleus awaits a more complete, and preferably cinematographic, comparison.

6. Adequate clinical description and pathologic study will continue to be of value in elucidating the genesis and nature of this remarkable symptom.

(Author's abstr.)

EEG Studies on Induced and Excised Epileptogenic Food in Monkeys.

In *rhesus* monkeys the application of a lumina cream to the motor cortex of one side produced a primary focus of EEG abnormality, characterized chiefly by delta activity, random spikes and sharp formations. This abnormality appeared prior to the onset of jacksonian attacks, which could be elicited by physical stimulation. Subsequently, a secondary (mirror) focus of EEG abnormality developed in the opposite motor cortex, which was followed later by generalized convulsions.

A direct correlation was found between the degree of EEG abnormality and the convulsive threshold. Maximal EEG disturbance was usually associated with generalized convulsions. Minimal EEG abnormality was associated with jacksonian attacks and was also present after the cessation of seizures.

Ablation of Area 4 resulted in eventual cessation of seizures and diminution of EEG abnormalities.

The limiting intravenous convulsant dose of metrazol for monkeys exhibiting epileptic seizures, or for similarly prepared monkeys after ablation of the primary focus, or for a monkey in which alumina cream had been applied subcortically, was significantly lower than that for control monkeys. (Authors' abstr.)

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Traits Related to Improved Adjustment of Psychotics after Lobotomy.

An investigation of the relationships between 199 behavior traits and improvement after lobotomy in 71 hospitalized patients produced evidence of significant association for only 12 traits. Nineteen traits in which statistical relationship was not significant were considered of interest on a purely rational basis. It is argued that the traits considered can be readily classed under two principles of prediction: (1) A heightened activity level is favorable to improved social adjustment after lobotomy. (2) Evidence of cortical domination of efferent pathways is favorable.

A scoring system based on 31 trait items makes a rough prediction possible. In terms of this system the investigator found a critical score above which the operation seems advisable; a lower critical score permits a more cautious prediction of no improvement. (Author's abstr.)

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" In this study five forms of the Army Alpha Group Examination were given to 15 mental patients whose intellectual level and formal schooling were, on the average, above those of the general population. With but few exceptions one test was given: (1) one day after the first shock, (2) one day after the 9th or 10th shock, (3) one day after the 19th or 20th (last) shock, (4) one week after the last shock, (5) about 3 weeks after the last shock." The results indicated a significant decline in test scores from the beginning to the end of the course of shocks, with a significant rise during the time after the termination of shock treatment. It was not possible to evaluate the final scores in terms of pre-illness test level because of the lack of data for these patients covering that period. In some instances where such information was available, the pre-illness test level seemed to be regained within a month after the end of the convulsive therapy.

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The Electroencephalogram in Epileptic Patients Aged 5 to 80 Years.

An analysis was made of the electroencephalographic findings in 369 cases of epilepsy (243 idiopathic and 126 symptomatic), aged five to 80 years, between periods of seizures.

Of the 146 patients under 20 years of age, 101 had idiopathic and 45 had symptomatic epilepsy.

Of the idiopathic group the EEG was aberrant in 91 per cent., with wave and spike forms accounting for 27 per cent.

Of the symptomatic group the EEG was aberrant in 60 per cent., with wave and spike forms accounting for 22·2 per cent.

For the combined total of epileptic patients in this age-span the incidence of aberrant EEGs was 80·8 per cent., with wave and spike forms accounting for 25·3 per cent.

Of 223 patients aged 20–80 years, 142 had idiopathic and 81 had symptomatic epilepsy.

Of the idiopathic cases the EEG was abnormal in 63·3 per cent., with wave and spike forms accounting for 16·4 per cent.

Of the symptomatic cases the EEG was abnormal in 54·3 per cent., with wave and spike accounting for 3·7 per cent.

For the combined total of epileptic patients in this age-span the incidence of abnormal EEGs was 61·1 per cent., with wave and spike accounting for 11·6 per cent.

On the whole, there was a lesser incidence of electroencephalographic abnormality among symptomatic than among idiopathic cases. Up to the age of 25 years, in cases of either idiopathic or symptomatic epilepsy, wave and spike forms showed a significantly higher incidence among younger patients. After the age of 25 years the symptomatic group showed a negligible incidence of wave and spike abnormalities, whereas the idiopathic group still displayed an appreciable, although waning incidence of wave and spike forms.

When the electroencephalographic abnormalities consisted of wave and spike forms, the case was more apt to be idiopathic, whereas when the abnormality consisted of either unilateral asymmetry, or generalized or isolated spikes, the case was more apt to be symptomatic epilepsy. (Authors' abstr.)

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A Case of Musicogenic Epilepsy.

1. The development of a specific musical stimulus to fit production is described in an epileptic woman.

2. Extensive clinical investigations failed to reveal an acquired cerebral lesion, although the fit pattern, optokinetic response, and inter-seizure EEG indicate an epileptogenic area in the left temporal lobe.

3. Increases of blood pressure, heart rate, and respiration while listening to music were observed in this patient. These were associated with overt signs of emotion.

4. Fits could not be induced by pure tones, although the patient felt emotional to a tone of 512, which persisted, and was varied in loudness. Different kinds of music were invariably followed by a fit within five minutes.

5. Electroencephalographic studies showed a constant pattern for the development of the fit. No change of rhythm was seen while music was played before the fit began. The cortical discharge began six or seven seconds after the clinical onset. This discharge consisted of 6 c/sec. low voltage potentials having bilateral synchrony, steadily increasing in voltage and falling progressively in frequency to reach 2½–3 c/sec.

6. The possible mechanisms of fit production are discussed.

(Authors' abstr.)

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Inactivation of Certain Neurotropic Viruses in Vitro by Serum Lipides. Casals, J., and Olitsky, Peter K. (Rockefeller Inst., New York, N.Y.). [*Science*, **106**, 267–8 (1947).]

Serum lipides from mice, rabbits, hamsters, and horses reduced the potency of St. Louis, Russian, Far East, and Japanese *B. encephalitis* viruses. The lipide fractions were obtained by acetone-ether or hot alcohol extractions, and were emulsified in buffer saline solution before incubation with virus (infected mouse brain suspension) at pH 7·0–7·2 and 37° for periods up to 24 hours. The viral inactivation took place also in the presence of serum protein at 2–4°, although more slowly. The inactivating agent was not dialyzable and withstood heating at 99° for 1 hour. Its ability to change surface or interfacial tension showed no correlation with its antivirus action. When serum was extracted in succession with acetone, Et_2O, and hot EtOH–Et_2O, each extract was effective against virus. Whole lipides from egg yolk were inactive, those from brain moderately active. Of various brain lipide fractions, the acetone extract was markedly active, the Et_2O and hot EtOH–Et_2O extracts were only moderately so. The results may have bearing on the neutralization test for neurotropic viruses, and on chemotherapy of infections by them. MARION HORN PESKIN (Chem. Abstr.).

The Role of Acetylcholine in the Organism. Danielopolu, D. (Première clinique méd., Bucarest). [*Ann. méd.*, **47**, 121–8 (1946).]

The function of acetylcholine (AC) as a transmitter of nerve impulses is briefly discussed. In immunity processes the antigen in contact with the body cells liberates AC which in turn causes the production of globulins. The latter, in contact with the antigen, acquire the qualities of sp. antibodies. If the antigen is present in the organism for a longer time it causes an excessive formation of AC-precursor substance. Although AC is not a constituent of the antibody, it is in close connection with it. The introduction of antigen into the immunized organism causes the formation of the immunity complex, antigen-antibody-alexin, with the liberation of AC, the latter eliciting the anaphylactic shock. The types of antibodies that use alexins (cytolysins, bacteriolysins) cause reactions of an explosive nature. Other antibodies, like agglutinins, antitoxins, and precipitins, do not require alexins and act slowly with limited AC release. If the antigen is introduced into the organism in quantities too large to be destroyed by the antibodies, then a part is incompletely disintegrated and a sp. " apotoxin " is formed, which causes the symptoms of the disease. The development of the disease determines a second phase of immunity formation. Increased metabolism, as produced by infection, involves a higher consumption of AC which leads to tachycardia. When the immunity process has increased the AC production sufficiently to obtain adequate immunity, a shock, corresponding to the crisis in pneumonia, sets in, characterized by hypotension, bradycardia, eosinophilia, leucopenia and monocytosis. The defense mechanism of an organism is determined by the ratio of AC formation and cholinesterase. Eserine inhibits cholinesterase and also adrenolytic factors. The digitalis glycosides have the same action. Consequently digitalis should not be used as an exclusive cardiac agent but as a means of raising the " vegetative tonus." Eserine could serve the same purpose but its action is of too short duration. Both drugs favor the anaphylactic shock, which is prevented by atropine. The simultaneous application of digitalis with imunizing agents leads to increased immunity. It is admitted that histamine plays a role also. It is liberated by the action of the apotoxins on tissues. A. E. MEYER (Chem. Abstr.).

The Effect of X-rays on the Vegetative Nervous System. Nemenov, I. M. I. (Central Roentgenol. Radiol. Cancer Inst., Moscow). [*Am. Rev. Soviet Med.*, **4**, 446–8 (1947).]

Radiation therapy is of value in ulcerative diseases, jejunal ulcer, hypertension, Basedow's disease, and pericolitis complicated by severe constipation. The favorable effect on gastric ulcer and gastric crisis depends on the action of X-rays on the vegetative nervous system. Sugar and Ca contents of the blood are stabilized when either too high or too low, and gastric hyper- or hypoacidity is regulated. No changes were observed in patients who had a normal blood sugar or Ca, or a normal HCl in the gastric juice. In certain cases of chronic eczema with disturbed equilibrium of the vegetative nervous system, radiation was of value when administered to the corresponding segments of the spinal cord, as well as of the hypothalamus. W. R. Henn (Chem. Abstr.).

Development of Nervous Activity and Chemical Factors of Nervous Activity in Cats. Kakushkina, E. A. [*Byull. Eksptl. Biol. Med.*, **22**, *No.* 7, 65–7 (1946); *cf. C. A.*, **40**, 7242².]

The amount of acetylcholine-like material and of acetylcholine esterases was determined for the cerebral hemispheres of cat embryos of various lengths, for new born kittens and for kittens 2, 5, 7, 11 and 20 days old and for kittens 4 months old. The increase in acetylcholine-like materials is not a linear function of growth. Values for acetylcholine in γ were: for 5·5-cm. embryo 0·30, for 8-cm. embryo 0·23, for a kitten 2 days old 0·90, for 5 days old 0·60, for 7 days old 0·70, for 11 days old 0·54, for 20 days old 0·32 and for 4 months old 0·40. Esterase development did not follow the same pattern as growth in acetylcholine-like materials. Activity of esterases as measured by the amount of acetylcholine in γ increased throughout embryonic life and reached a maximum in the kitten 2 days old. Even at 4 months the degree of activity of esterase as measured by the acetylcholine destroyed in 15 minutes (0·45 γ) was larger than the maximum found in embryonic life (0·17 γ) in the case of the 8-cm. embryo, but was not as great as in the newborn cat (0·72 γ). N. M. P. (Chem. Abstr.).

The Occurrence of Citrate in Human Cerebrospinal Fluid with Special Consideration of the Difference between the Citrate Content found by Lumbar and by Subarachnoid Puncture. Benni, Bertil, Larsson, Hans, and Thunberg, Torsten. (Univ. Lund, Sweden). [*Kgl. Fysiograf. Sallskap. Lund, Forh.*, **13**, 91–7 (1943) (*Pub.* 1944) (*in German*) : *cf. C. A.* **24**, 4549, 5827.]

Normal values for citric acid (I) in cerebrospinal fluid (II) (in γ per ml.) were 45–55, as determined by the methods of Pucher *et al.* (*cf. C. A.*, **30**, 2597⁸) and of Thunberg (*C. A.*, **27**, 5770). The average normal value was 50. In meningitis, syphilitic nerve diseases and vascular lesions, (I) increased to 50–100 (or more). Lower values occurred in epilepsy, hydrocephalus, and brain tumors with increased intracranial pressure, but (I) was never totally absent from (II). Amounts of (I) in the (II) of the following numbers of epileptics were : 4 (under 30), 19 (31–35), 10 (36–40), 7 (46–50). The arithmetrical average value was 31 γ per ml. The amount of (I) in normal serum is 20–25, about half the amount in (II). Ratios between various constituents in serum and in (II) are discussed. Ca and Mg are probably present to some extent as complex univalent " calcitrate " and " magnecitrate " ions, respectively. Average values for the amount of (I) in (II) in different diseases by subarachnoid and by lumbar puncture, respectively, were: acute encephalitis, 40, 53; chronic encephalitis, 39, 56; epilepsy, 34, 47 ; cerebral hemorrhage, 35, 58 ; cerebral arteriosclerosis, 36, 72 ; hypertonia, 28, 53 ; cerebral tumor, 49, 63 ; cephalalgia, 28, 51. Average values for all the pathological conditions were 36 and 57, respectively. Results are discussed but without any very definite conclusions. W. C. Tobie (Chem. Abstr.).

Certain Hormones in the Cerebrospinal Fluid. Myasnikov, A. L. (*Naval Med. Acad., Leningrad*). [*Klin. Med.* (*U.S.S.R.*), **23**, *No.* 12, 156–63 (1945).]

Intravenous injection of freshly drawn spinal fluid (5–10 c.c.) in human cases leads to a sharply raised blood-sugar level, i.e. the action is similar to that of the

hypophysis hormones. The rise is of the order of 20–5 mgm. per cent. and lasts about 2 hours. The donors showed a significant drop of the sugar level, which was especially pronounced in diabetic patients where drops of 50–150 mgm. per cent. over several hours were observed. The recipients showed in some cases a slight rise of blood pressure although if the donor was a hypertonic individual, the blood pressure of the recipient gave a fairly pronounced rise for several hours. The pressor effect was also given by donors with diabetes or acromegaly. Since the pulse is not affected, the hormone involved is not the adrenotropic hormone. The donors gave an opposite picture of blood-pressure variation, but also showed a distinct rise of blood cholesterol, which levelled off within 3 hours. The greatest changes again occurred in diabetic patients. The effects described are linked to hypophysis hormones which penetrate into the spinal fluid.

G. M. Kosolapoff (Chem. Abstr.).

The Pituitary Gland and Carbohydrate Metabolism. I. The Posterior Lobe. Corkill, A. B., and Nelson, J. F. (Baker Med. Research Inst., Melbourne, Australia). [*Med. J. Australia*, **34**, 130–4 (1947).]

The antagonism between posterior pituitary lobe extract and insulin on blood sugar was studied in cats, usually under amytal anaesthesia but sometimes under spinal. Eviscerated preparations were sometimes used. Posterior pituitary extract "surgical," which was employed, appeared to provoke a secretion of adrenaline which counteracted the insulin hypoglycemia.

II. *The Anterior Lobe. Ibid.*, 172–4.—The effects of anterior pituitary extract and insulin on glycogen and sugar content of the rat diaphragm musculature was studied by means of a modified Gemmel technique previously described. The initial glycogen content of muscles in rats treated with anterior pituitary extract was lower than in normal muscles. In Ringer's solution without insulin 90 per cent. of the glucose that disappeared could be accounted for by oxidation. With insulin, the extra glucose disappearing in the muscle strips could be accounted for by the deposition of muscle glycogen. The amount of glucose that disappeared from the strips of muscle prepared from rats treated in the absence of insulin with anterior pituitary extract was of the same order as that observed in normal animals. These findings are discussed. G. H. W. Lucas (Chem. Abstr.).

Disturbances in the Autonomous Nervous System in B_1-avitaminosis. Selezeneva, I. A. A. [*Farmakol i Toksikol*, **10**, *No.* 2, 3–6 (1947).]

Functional changes were studied in the neuromuscular system of B_1-avitaminotic rats with the Magnus method. Adrenaline (I), acetylcholine (II), and $BaCl_2$ (III) were tested for depressant and paralytic effects on the autonomous innervation system of intestinal musculature. A direct relation was observed between neuromuscular effect and duration of avitaminosis. There were 3 test groups: 10 rats, 4 months of B_1-free diet; 5 rats, 1 month; 5 controls, normal diet. Drug concentrations in p.p.m. were: (I), 0·005, 0·0067, 0·01, 0·02; (II), 0·002, 0·004, 0·005, 0·0067, 0·01, 0·02; (III) 12·5, 16·7, 25. Serious depression of autonomous intestinal innervation was observed; the effects of (I) and (II) indicate, in addition to inhibition or paralysis of receptor activity, a high content of adrenoxidase and cholinesterase. Julian F. Smith (Chem. Abstr.).

Cholinesterase. Bodansky, Oscar (Edgewood Arsenal, Md.). [*Ann. N.Y. Acad. Sci.*, **47**, *Art.* 4, 521–47 (1946).]

Recent data on cholinesterase (I) suggest there is not 1 or 2 types of (I) but rather a "family" of enzymes which in a general way can be divided into 2 groups. The division is made on the basis of their reaction to increasing substrate concentrations (I) in sera and some tissues obey the Michaelis-Menton formulation while the (I) in red cell and brain are inhibited at higher substrate concentrations of acetylcholine. The effects of pH and various ions on (I) are discussed. Disagreements in the literature are resolved if it is remembered that the studies were carried out on (I) from different sources. The *in vitro* action of various (I) inhibitors is summarized. The sensitivity of (I) to inhibition by diisopropyl fluorophosphate (II) varies, depending on the source, (I) from rabbit serum requiring about 1/10,000th as much (II) as the other sera studied to give 50 per cent. inhibition.

Administration of (II) to monkeys gave no symptoms even when the serum (I) levels was reduced to zero ; severe toxic symptoms are associated with zero levels of brain (I) activity. Recovery of brain (I) in rabbits poisoned with (II) is exceedingly slow. The inhibition of (I) by (II) is irreversible since dilution or dialysis does not increase activity of (I) inactivated with (II). Attempts to classify (I) from various sources into types such as specific or true and nonspecific or pseudo lose their significance when the comparisons are made using additional criteria such as sensitivity to (II) or activity against triacetin. There is no evidence to suggest that the low serum (I) values found in debilitating diseases are of any special significance, so far as transmission of nervous impulses is concerned.

Carl C. Smith (Chem. Abstr.).